The New England
Journal of Medicine

Copyright, 1949, by the Massachusetts Medical Society

Volume 240 APRIL 14, 1949 Number 15

THE OCCURRENCE OF INFECTION AFTER PULMONARY RESECTION

A Study of the Effectiveness of Sulfonamides and Antibiotic Agents During a Six-Year Period (1942–1947)

CARROLL C. MILLER, M.D.,* AND RICHARD H. SWEET, M.D.†

BOSTON

AN ANALYSIS has been made of 427 cases of pneumonectomy and lobectomy during the years 1942 through 1947 at the Massachusetts General Hospital, and the results of the use of chemotherapeutic and antibiotic agents have been tabulated, with particular regard to complications caused by infection and to mortality. With few exceptions these complications occurred and were recognized during the postoperative hospitalization period; in several cases late recrudescence or fulmination of symptoms required readmission and further treatment. The latter cases have been included in the present study because the complications were considered to be the direct result of operation and its associated therapeutic program.

The years 1942 through 1947 were chosen because it was during this period that sulfonamides were first used, then penicillin and more recently streptomycin with increasing frequency. Sulfonamides were at first given in only a relatively small proportion of cases, and the manner in which they were administered in many cases would not be considered adequate in the light of the present concept of effective chemotherapeutic bacteriostasis. In 1944, when penicillin became available, the trend toward more complete prophylaxis and therapy was well under way, and by the end of 1946 all patients received penicillin. During the year 1946, a few selected patients received streptomycin in addition to penicillin, and in 1947 about half the patients received both drugs. It is the purpose of this study to show the definite decline in the rates of mortality and empyema during this six-year period as correlated with the use of chemotherapeutic and antibiotic agents.

In addition to the use of sulfonamides, penicillin and streptomycin during these six years, another factor contributes strongly to the improvement in postoperative results. This is the diminishing use of the tourniquet in lung resections, and the adoption of the individual ligation technic in dealing with hilar structures. Such a technic was adopted before 1940,[1] and in the beginning of the series of cases reported here, the number of resections performed by the tourniquet method was already small. Later, in the past three years, the tourniquet and mass ligatures were never used as a method of controlling the hilus *en masse* proximal to the point of resection. In a very few cases it was necessary to employ the tourniquet temporarily to permit the removal of the lobe or lung; after this step the individual bronchovascular structures were isolated and separately secured. Judging from the high incidence of complications following the use of the tourniquet, and in recent years the infrequent occurrence of empyema with bronchopleural fistula or of massive fatal hemorrhage with the individual ligation technic, a distinct and significant, favorable influence may be attributed to the latter method. In recent years, another detail of technic used routinely at the hilus has been the careful suture of the bronchus with a single row of interrupted fine-silk sutures and complete capping of the closed stump with a pleural flap.[2]

Because of the diversity of diseases of the lung treated by resection and the number of different procedures performed, a mass grouping of all cases is of little significance except to give an over-all picture of results in a thoracic surgical service. On the other hand, a division of these cases into small sub-groups produces many series with no great importance from a long-range point of view. The value of individual group study, however, lies in the comparison afforded between the results of treatment in various diseases, and between different resection procedures (pneumonectomy, total lobectomy and segmental lobectomy in the various

*Assistant in surgery, Harvard Medical School; assistant in surgery, Massachusetts General Hospital; surgeon, Palmer Memorial Hospital; attending physician in thoracic surgery, Cushing Veterans Administration Hospital, Framingham, Massachusetts.

†Associate clinical professor of surgery, Harvard Medical School; visiting surgeon, Massachusetts General Hospital.

lobes). A suggested prognosis in each type of case is thereby offered.

Four major disease groups are considered. These are bronchiectasis, lung abscess, tuberculosis and carcinoma. As indicated in Figure 1, lobectomy for bronchiectasis in the years 1943, 1944 and 1946 was associated with no mortality in 60 cases and with a total mortality for the six years of 3.9 per cent; in this group there were 4 cases of empyema in 1943, 1 in 1944, 3 in 1945, and none in 1946 or 1947. Lung abscess was associated with a relatively high incidence of complications, but improvement is seen in the last two years. This incidence contributes mainly to the striking increase of empyema in all cases in 1943. In the most recent report on the treatment of lung abscess at the Massachusetts General Hospital, the importance of

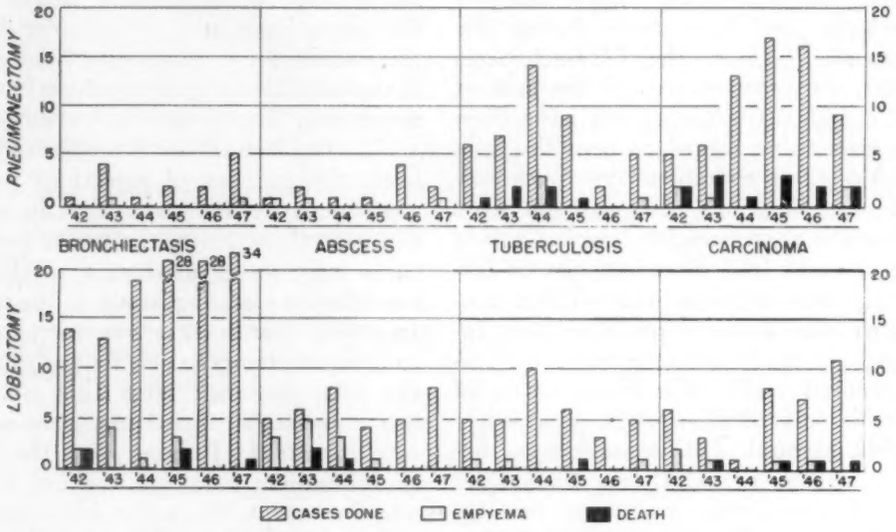

FIGURE 1. *Incidence of Empyema and Death Following Pneumonectomy and Lobectomy, Arranged in Groups of Bronchiectasis, Abscess, Tuberculosis and Carcinoma and Further Subdivided into Yearly Blocks.*

lobectomy in selected cases was discussed as a more desirable method of treatment than drainage.[3] As a result of the adoption of this policy, more lobectomies and pneumonectomies have been performed for this disease in the past few years. The tuberculosis data are essentially those reported in 1946, with the inclusion of the rest of the cases in that year and those in 1947, subsequent to that report.[4] The cases of carcinoma bring into consideration other factors (resection for palliation, general condition of the patients and complicating infection) that may influence death and empyema rates, but they are not within the specific scope of this paper.

Figure 2 shows the improvement in empyema rates and death rates for lobectomies and pneumonectomies as separate groups coincident with the use at first of sulfonamides and later of penicillin and streptomycin. In six years the gross mortality rate for all diseases treated by pneumonectomy and lobectomy dropped from 21.4 per cent and 8.3 per cent to 8.7 per cent and 2.9 per cent respectively; in 1947 none of the deaths were due to sepsis but instead to technical difficulties during operation (uncontrollable hemorrhage and plugging of contralateral bronchial tree with mucus or blood) and in 1 case to later cardiorespiratory failure manifested at autopsy by pulmonary congestion and edema. In the first five years, through 1946, the empyema rate similarly dropped from 21.4 per cent and 27.7 per cent to 3.7 per cent and 2 per cent respectively. In 1947 there were 5 empyemas in the group of 23 pneumonectomies (21.7 per cent) and 1 empyema among 68 lobectomies (1.5 per cent). Three of these, which were total empyemas subsequent to pneumonectomy, became evident several months after discharge following an apparently smooth convalescence. During these operations there had been no unusual, obvious contamination. Of the 5 empyemas complicating pneumonectomy, 2 were after operations for carcinoma, and 1 each after operations for abscess, bronchiectasis and tuberculosis.

Figure 3 demonstrates the same trends shown in Figure 2, but in simplified detail and in a different combination of data. During the six-year period the improvement in *death* rate after pneumonectomy, lobectomy and in the total number of resection cases grouped together is readily seen. A similar decrease in the *empyema* rate is obvious.

Figure 4 shows the total number of deaths during the six years as compared with the number of deaths associated with empyema. In 1944 it is seen that half the patients (2 out of 4) who died had

empyema, but thereafter there was a decline to 0. It should be stated at this point that during the period 1942–1947 the procedures were carried out by several operators of varied experience, and this fact may also have influenced the statistical results.

Lobectomy for bronchiectasis presents the best immediate postoperative prognosis of all the diseases in experienced hands (Fig. 1). With the continued trial of segmental resection methods, there may be a variation in the complication-rate curve. It has been our experience that patients who undergo a segmental resection do not have so smooth a convalescence as those who undergo total lobectomy [5, 6] This discrepancy seems to be due less to immediately resultant infection than to technical intrapulmonary or intrapleural factors such as infarction of a lobar segment by inadvertent interruption of a major blood vessel to that segment, plugging of a bronchus with resulting atelectasis, inadequate aspiration of the bronchial tree during or after operation, com-

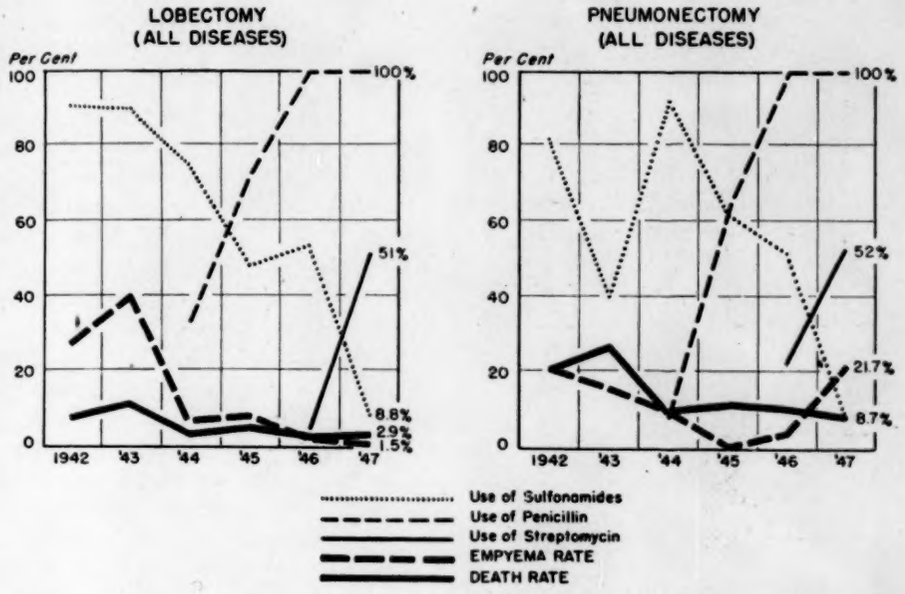

FIGURE 2. *Incidence of Empyema and Death in Relation to the Use of Sulfonamides, Penicillin and Streptomycin.*

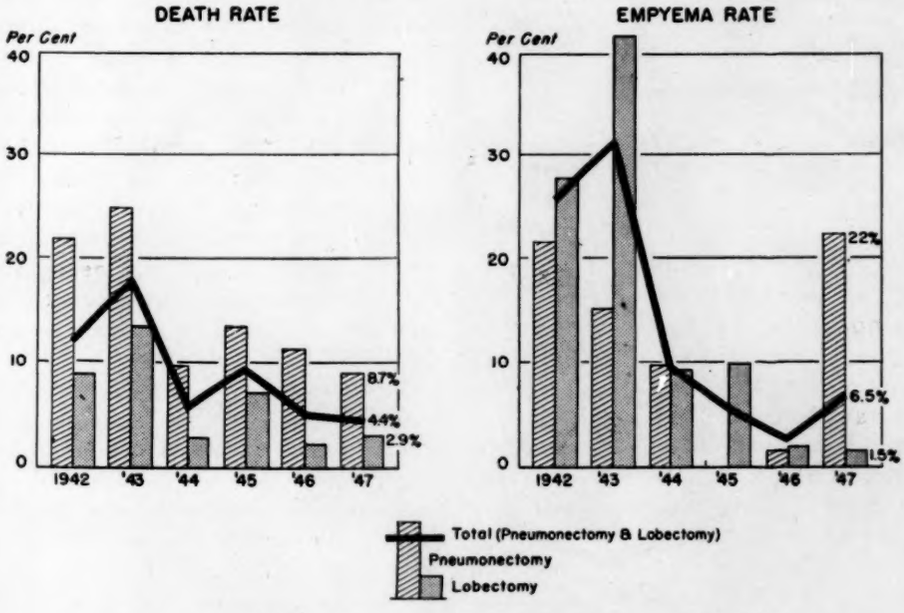

FIGURE 3. *Mortality and Empyema Rates for Pneumonectomy and Lobectomy.*

pression atelectasis by accumulated pleural effusion, too extensive suturing of lobe surfaces in order to obtain pleuralization or hemorrhage into lung parenchyma beneath the suture line. Recently, according to the suggestion of other writers,[5, 7, 8] several of the surgeons in this hospital have been either leaving the cut surface of the remaining segment of lung uncovered by pleura or using a circumferential marginal flap of pleura left purposely on the remaining segment during resection to be sutured over the raw parenchymal surface. The patients in whom this detail of technic has been used have appeared to recover more uneventfully than

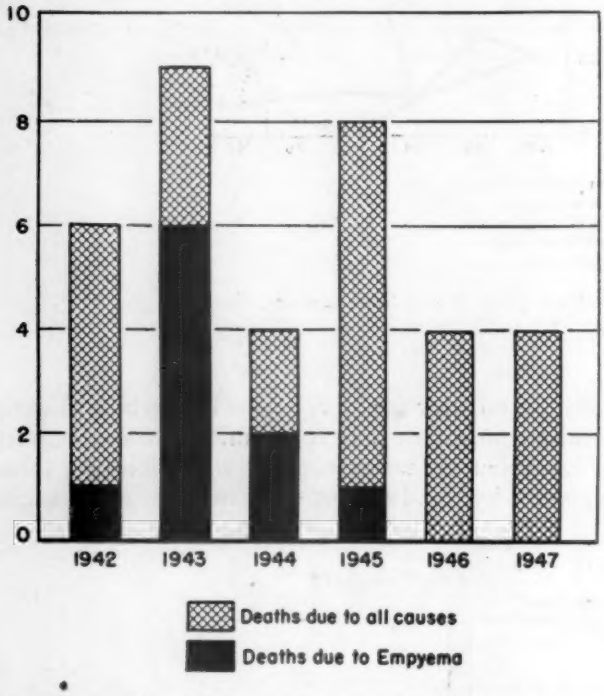

FIGURE 4. *Total Number of Deaths for Each Year Compared with the Number of Deaths Complicated by Infection.*

many of those in whom the clamp-suture or nonstripping technic has been employed.

It should be emphasized that in the majority of cases of bronchiectasis, lung abscess or tuberculosis there is a mixed infection, involving organisms that may be resistant to currently available drugs. The development of more effective agents may be necessary to obtain better results. For example, streptomycin has been used together with penicillin, both in supposedly adequate large doses in a number of such cases. It was interesting to observe that often in these cases there was no demonstrable response to drug therapy as indicated by the temperature chart preoperatively. After operation, however, the course was extremely smooth, with no complications. This suggests that the most important factor of treatment is the extirpation of diseased tissue. On the other hand, protection with chemotherapeutic and antibiotic agents is a valuable safeguard because although healing of the lesion may not occur without the benefit of surgery, the surrounding pneumonitis can be appreciably reduced as shown by roentgenograms, and spreading invasive infection, empyema and wound sepsis may be prevented in a large majority of cases.

In patients with wet bronchiectasis, the use of aerosol penicillin has reduced the amount of sputum and increased the patient's sense of well-being.[9] This effect is somewhat more marked when penicillin is nebulized and inhaled than when it is given by intramuscular injection alone. (Aerosol streptomycin was administered with aerosol penicillin to 15 patients in the whole series.)

Mention should also be made of the use of penicillin and streptomycin injected into the pleural cavity after the demonstration of frank empyema. Two cases in this series were cured in this way without rib resection for drainage, one with penicillin and one with streptomycin, and 4 others were unsuccessfully treated. Such therapy must be early, massive (at least 100,000 units of penicillin or 1 gm. of streptomycin, or both, daily) and persistent until the infection is controlled. As repeatedly emphasized in the recent and current literature, when a persistently recurring accumulation of pleural fluid following lobectomy or pneumonectomy is shown by culture, or by direct smear at the time of thoracentesis, to be contaminated by bacteria, penicillin or streptomycin, or both, depending on the nature of the infecting organisms, should be injected immediately and the therapy continued daily. The injection should be preceded by the aspiration of as much of the exudate as possible. It is important to institute this regimen early since, especially in cases of lobectomy, after three or four days the effusion may become loculated by the fibrinous process within it, and it is no longer possible to treat the empyema as a single cavity. During the diminution in amount of fluid as demonstrated by roentgenograms and the results of aspiration, and when the febrile reaction subsides, this medication can be administered less frequently and presently stopped.

The presence of a bronchopleural fistula that complicates an empyema suggests the interesting query, Is the fistula the cause or the result of the empyema, and how effective can specific bacteriostatic medication be in the presence of an open bronchial stump? An immediate, obvious answer is that if the bronchial suture line opens and remains open, contamination will occur and persist in spite of the use of antibiotic agents. This, it is believed, is not necessarily the case. If bacterial activity in the vicinity of a bronchial stump is adequately inhibited by the drug employed by virtue of both its systemic and its intrapleural concentrations, and if tissue healing proceeds at a normal

rate, the bronchial fistula may well heal before the process becomes a chronic one. Thus, it is clearly indicated that satisfactory antibiotic protection must be combined with a careful technic and a thoroughly supportive nutrient regimen.

In this whole series, there were reported 11 bronchopleural fistulas, 1 in 1942, 7 in 1943, 2 in 1944, 1 in 1946, and 2 in 1947. The one patient in 1946 received penicillin before and after operation, and healed his fistula spontaneously within two weeks. The others in previous years received only sulfonamides, and in those who survived, healing was slow and prolonged. One of the 2 patients in 1947 who developed a fistula had had a pneumonectomy for tuberculosis and was given penicillin before and after operation, and streptomycin postoperatively only. The other, a patient who had a pneumonectomy for bronchiectasis, received penicillin intramuscularly and by the aerosol route preoperatively, in the chest at operation, and intramuscularly postoperatively — and streptomycin, only at operation, in the pleural cavity. The former was discharged to a sanatorium with the fistula still patent, and the latter required first a rib resection for drainage and later a thoracoplasty. Patients who developed fistulas in other years also had protracted convalescences.

The trend in fistula development closely follows that of empyema, and the problem of prevention should entail, in addition to the technic of closing the bronchus, the prophylactic and therapeutic principles used in the prevention or cure of infection in general.

A survey of pneumonectomy and lobectomy cases combined, with respect to sulfonamide, penicillin and streptomycin administration, reveals that in 1942, 6 patients received no drug therapy, and of these, 1 had empyema; in this group in which the drug *was* used there seems to be little or no correlation between the method of administration and the incidence of empyema. Twenty patients received a sulfonamide in the pleural cavity at operation and by parenteral administration postoperatively, and 5 had empyema. Twelve received it postoperatively* only, and 3 had empyema. Two received it preoperatively and postoperatively with no empyema. Seven received it in the pleural cavity at operation only, and there were 4 empyemas. One received it preoperatively and in the chest without resulting empyema. One received it preoperatively only and had empyema. One received it by all three methods and had empyema. Of the 3 fatal cases with infection in the form of empyema or parenchymal sepsis, none had what would now be called an adequate dosage of sulfonamide. Of course, these data are influenced strongly by the type of case (Fig. 1), but a general conclusion from the group as a whole indicates unsatisfactory protection with sulfonamides.

In 1943, a single case of empyema occurred among 15 patients who received no sulfonamide. Sixteen received the drug postoperatively, with 5 empyemas. Ten received it before and after operation, with 4 empyemas. In 4 it was used in the chest and postoperatively, with 3 empyemas. In 4 it was used preoperatively and postoperatively and in the chest, with 3 empyemas. Two received it preoperatively, with no empyema. Three of the 6 patients who died from sepsis had sulfonamide before and after operation, and of these, 1 received sulfanilamide in the pleural cavity at operation. The remaining 3 had it only postoperatively. The comment made in the above paragraph applies also to the year 1943, but the ineffectiveness of sulfonamides becomes more apparent.

In 1944 there were 2 cases of empyema among 56 patients who received sulfonamides alone, but on detailed analysis, the drug was given much more adequately than in previous years. Eleven had penicillin alone, with 2 empyemas, and 6 had both penicillin and sulfonamide, with 3 empyemas (the penicillin dosage and time of administration were inadequate). Sulfonamide was used in the chest at operation only once during this year and never thereafter. The 4 patients who died received a sulfonamide before and after operation, and 2 of these were given penicillin late in the postoperative period, but to no avail. Two of the 4 had definite empyema; in the remaining 2, pneumonia was suspected but not proved.

In 1945 sulfonamide alone was given to 23 patients, with 1 empyema, the drug, again, having been administered more thoroughly in most cases. Thirty-nine patients had penicillin alone, with 4 empyemas. Twenty-three had both, with no empyema. The 1 patient who apparently died of sepsis received sulfonamide preoperatively and postoperatively but no penicillin.

In 1946 penicillin alone was administered to 35 patients, and 1 developed empyema, which was cured by postoperative intrathoracic injection of penicillin. Forty-one received both penicillin and sulfadiazine, and there was 1 empyema. In this year 4 patients received streptomycin by aerosol administration preoperatively, and intramuscularly postoperatively, and an additional patient had it instilled in the chest at operation only. None of these had sepsis complicating recovery, and there were no deaths from sepsis.

During 1947, a year in which 6 cases were complicated by empyema, *all* patients (91) were given penicillin at some time during their hospital course, either before or after operation, or both. Some received aerosol penicillin before, and some after, operation. A large majority (69 patients) received an intrapleural injection at the conclusion of operation. Streptomycin was used with penicillin in

*Unless specifically mentioned as being administered intrapleurally, or "in the chest," these drugs were given orally or intravenously (sulfonamides), or intramuscularly (penicillin and streptomycin).

the same manner of administration in 46 cases. Sulfonamides were given (without streptomycin) in 5 cases in the early part of the year before streptomycin became freely available, and in 3 additional cases with streptomycin as well. One of the latter patients received a sulfonamide postoperatively specifically for a bladder infection, and the other 2 had it preoperatively with streptomycin used only in the pleural cavity at operation.

A detailed analysis of the drug therapy given in the cases of empyema in 1947 indicates an inadequacy of streptomycin administration in the light of our present concept, for only 1 patient received streptomycin preoperatively and only 2 received it intrapleurally. (Four of the tuberculous patients some of these organisms to the medication given. In the cases of tuberculosis we have been particularly mindful of this problem when streptomycin has been given for a period of several weeks before proposed operation and when its use after operation has been planned. Sensitivity studies have usually been done in the sanatorium before the patient comes to us, and care has been taken to avoid prolonged administration with its danger of both desensitization of the organism and toxicity to the patient. In the nontuberculous patients, also, it is indeed probable that certain cases that responded poorly to antibiotics did so because of natural or acquired resistance of the infecting organisms. However, the over-all improvement seen

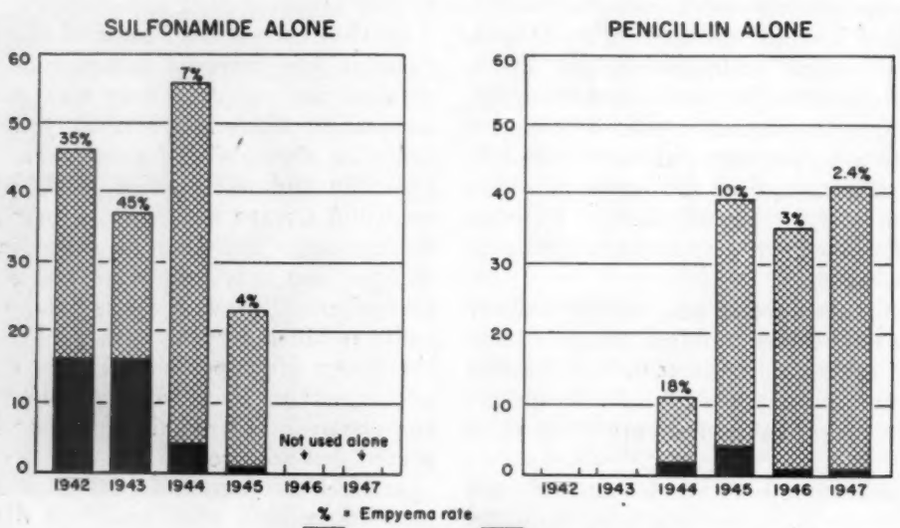

FIGURE 5. *Incidence of Empyema in Each Year, First with Sulfonamide Administration Alone, and Then with Penicillin Alone.*

were not given intrapleural streptomycin, but of these only 1 developed empyema.) Three of the 6 patients with empyema received penicillin adequately (according to present standards), but 2 received it only postoperatively. Five of these cases were pneumonectomies — for carcinoma (2), abscess (1), bronchiectasis (1) and tuberculosis (1). The 1 lobectomy was done for pneumatocele. In none of the cases was there any error in technic or untoward factors that had not been encountered many times previously. Thus, there seems to be at hand no satisfactory explanation for the disappointing rise (Fig. 3) in the empyema rate for pneumonectomy in this year as contrasted with that of the preceding three years.

Except in rare cases in the total group of cases reported here, studies of the sensitivity of infecting organisms to antibiotic substances were not done, and the agents used were administered empirically without specific regard for possible resistance of in this six-year period suggests that in general the sensitivity problem per se does not definitively affect the trend of results. In *most* cases the infecting organisms appear to be susceptible, or the antibiotic agent is not administered for a sufficiently long time to alter the sensitivity of the organism. On the other hand, more detailed attention to these factors should enhance the improvement already effected, and give a more accurate picture of the role that these agents play in certain refractory cases of postoperative infection.

The relative decline of empyema rate associated with the use of each of the two earliest chemotherapeutic agents alone (sulfonamide and penicillin) is indicated in Figure 5, in an attempt to evaluate the trend in the respective series. There is a more consistent drop to a lower level with penicillin than with sulfonamides. However, it will be noted that in 1944 and 1945, there was a higher incidence of empyema with penicillin alone than with sulfon-

amide alone — a fact that suggests that for optimum protection penicillin should be combined with a complementary agent.

Figure 6 demonstrates the gradual shortening of the hospitalization period in each year with the gratifying conclusion that in addition to the all-important improvement in postoperative results, a monetary saving for the patient and an increased availability of beds for the hospital are achieved.

The present routine chemotherapeutic program used for lung resection consists of the intramuscular injection of 300,000 units of penicillin (100,000 units every eight hours) and 1 gm. of streptomycin (0.25 gm. four times a day) daily for two days before operation. When there is fever or other signs and symptoms of toxicity, profuse sputum or evidence of pneumonitis by roentgenologic examination, penicillin may be administered for a week or ten days preoperatively. Aerosol penicillin, 50,000 units in 1 cc. of physiologic saline solution, with or without streptomycin (0.25 gm.) as indicated, is administered four times a day when expectoration is profuse preoperatively. In a few cases this form of chemotherapy has been used effectively in reducing the volume of sputum postoperatively. At operation, before the chest is closed, 100,000 units of penicillin and 1 gm. of streptomycin dissolved in 30 cc. of physiologic saline solution are instilled into the pleural cavity. Intramuscular injection of both drugs (100,000 units of penicillin and 0.25 gm. of streptomycin every six hours) is continued for five or six days, or until the patient's temperature chart has been normal for three days. The use of penicillin and streptomycin intrathoracically in the event of suspected empyema after operation has been described above. When infection is present either before or after operation, the dosage and frequency of administration are increased.

Since the conclusion of the period covered in this study, streptomycin has been administered in addition to penicillin in *all* cases of lung resection as a routine adjunct in therapy with the hope that the figures herewith presented will be improved in immediately succeeding years.

Summary and Conclusions

Four hundred and twenty-seven cases of lung resection at the Massachusetts General Hospital in a six-year period (1942–1947) are reviewed with the specific intent of demonstrating the trend of infection and mortality rates in reference to the use of chemotherapeutic and antibiotic medication. The incidence of empyema and septic deaths is especially stressed. Intrapulmonary infection postoperatively is not considered in detail because of the difficulty in determining the exact extent and nature of the lesion in cases that do not come to subsequent operation or autopsy. Wound sepsis has been practically nonexistent in this series of operations. Silk-suture material has been used almost invariably in the chest-wall closure.

The broad groups of lobectomy and pneumonectomy, as well as the four major disease entities in pulmonary pathology, — bronchiectasis, abscess, tuberculosis and carcinoma, — have been analyzed with respect to the obvious improvement in operative results. The data show a significant decline in infection and mortality rates, in the ratio of nonseptic to septic deaths and in the duration of hospital confinement for patients with uncomplicated and complicated postoperative courses.

Finally, a brief outline is given of the current regimen of protective medication used.

Chemotherapeutic and antibiotic agents seem to have a valuable place in the program of surgical treatment of pulmonary disease.

Drug therapy must be adequate and complete — that is, it must be given preoperatively and postoperatively. The use of penicillin and streptomycin in the pleural cavity at the conclusion of a resection cannot be easily evaluated, but it is assumed that it contributes to better results.

All cases must be carefully studied from a bacteriologic standpoint, and the proper agent and dose selected for the individual patient.

Early postoperative bronchoscopic aspiration should be used when there is failure of expansion as a result of bronchial obstruction, and prompt thoracentesis should be done in the presence of appreciable effusion. Intrathoracic instillation of

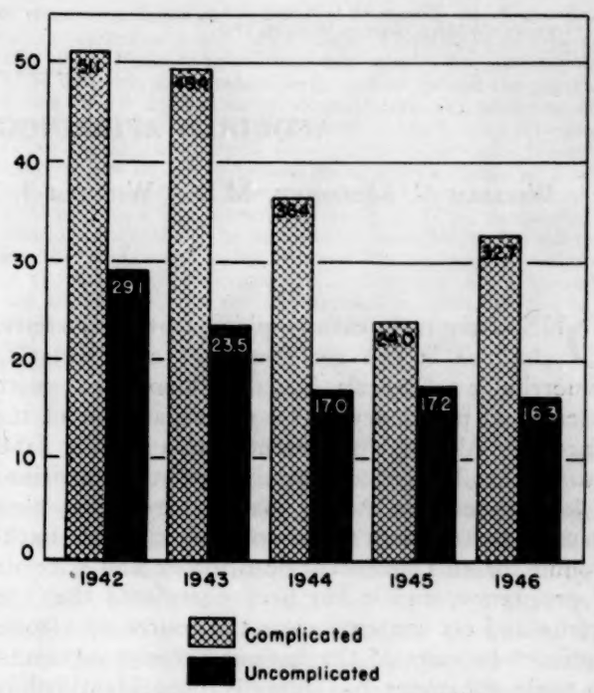

Figure 6. *Average Number of Days Spent in the Hospital after Lung Resection in Both Complicated and Uncomplicated Cases.*

massive doses of penicillin and streptomycin may be effective in preventing or curing empyema.

Aerosol penicillin with or without streptomycin is of benefit when sputum is profuse.

It is believed that these agents also minimize the tendency to the development of pneumonitis in atelectatic areas of lung tissue, which frequently occurs postoperatively.

References

1. Churchill, E. D., and Belsey, R. Segmental pneumonectomy in bronchiectasis: lingula segment of left upper lobe. *Ann. Surg.* **109**: 481-499, 1939.
2. Sweet, R. H. Closure of bronchial stump following lobectomy or pneumonectomy. *Surgery* **18**:82-84, 1945.
3. *Idem.* Analysis of Massachusetts General Hospital cases of lung abscess from 1938 through 1942. *Surg., Gynec. & Obst.* **80**:568-574, 1945.
4. *Idem.* Lobectomy and pneumonectomy in treatment of pulmonary tuberculosis. *J. Thoracic Surg.* **15**:373-383, 1946.
5. Overholt, R. H., Woods, F. M., and Betts, R. H. Improved method of resection of pulmonary segments: report of technique applied in 70 operations. *J. Thoracic Surg.* **17**:464-479, 1948.
6. Wandall, H. H. Personal communication.
7. Clagett, O. T., and Deterling, R. A., Jr. Technique for segmental pulmonary resection with particular reference to lingulectomy. *J. Thoracic Surg.* **15**:227-238, 1946.
8. Overholt, R. H., and Langer, L. New technique for pulmonary segmental resection: its application in treatment of bronchiectasis. *Surg., Gynec. & Obst.* **84**:257-268, 1947.
9. Findlay, C. W., Jr., and Sweet, R. H. Aerosol penicillin as therapeutic adjunct in preparation of patients with suppuration of lung for pulmonary resection. *J. Thoracic Surg.* **16**:81-90, 1947.

ACQUIRED AFIBRINOGENEMIA IN PREGNANCY*

William C. Moloney, M.D.,† William J. Egan, M.D.,‡ and Arthur J. Gorman, M.D.§

BOSTON

ONE of the most catastrophic events in obstetric practice is the occurrence of a fulminating hemorrhagic diathesis usually associated with toxemia of pregnancy and toxic separation of the placenta. Although uncommon, this usually fatal disorder has been encountered by most obstetricians of long experience.[1-3] For many years it has been suspected that there was a common etiologic background for this hemorrhagic disorder and toxemia of pregnancy, and it has been postulated that the uterus and its contents were the source of a toxic factor.[3-6] In spite of the various theories advanced no toxic substance has actually been identified in the blood of patients with toxemia of pregnancy.

Although the occurrence of incoagulable blood, in what has been called the "calamitous" toxemic patient, has been described by a number of authors,[2, 3] the characteristics of the defective clotting mechanism have not been clearly established. Recently, a patient was encountered with this hemorrhagic disorder in pregnancy, and the following report is an account of the case with certain observations on the nature of the incoagulability of the blood.

Case Report

Mrs. T. W., a 25-year-old gravida II, whose estimated date of confinement was January 30, 1948, entered the hospital because of lower abdominal pain and bleeding from the gums. She had been well throughout her pregnancy except for a prior admission to the hospital at about the 8th month for lower abdominal pain. At that time after 48 hours she was discharged with a diagnosis of false labor; the blood pressure and urinary findings were within normal limits. Throughout the last month of pregnancy she had lower abdominal discomfort and some dull pain, but at no time was there elevation of the blood pressure or abnormal urinary findings.

On the evening of January 31 the lower abdominal pain became more severe, and about 10:00 p.m. the patient noted spontaneous bleeding from the gums. Both the pain and bleeding from the gums became worse, and she was admitted to the hospital at 1:00 a.m. on February 1.

The past and family histories were free of any evidence of abnormal bleeding tendency. In general her health had been excellent except that at the age of 15 the gall bladder and appendix had been removed. The patient had had one prior pregnancy; 2 years before, she had given birth uneventfully to a full-term, normal child. There was no history of toxemia during the first pregnancy, but she had noticed slight bleeding from the gums.

The patient complained of severe lower abdominal pain, and the uterus was tense and painful to palpation. The fetal heart was not heard. An unusual feature was the obvious bleeding from the gums; there was no ulceration, but the gingival margins were slightly swollen and free bleeding occurred from these areas. At 4:00 a.m., after an obstetric consultation, the clotting time was found to be greatly prolonged. Two hours later the patient was in good general condition, but the bleeding from the gums was more profuse and it was noted that wherever injections or venipuncture had been performed, ecchymotic areas appeared. Moreover, the uterus seemed larger and more painful. At this time, more detailed blood studies were carried out. The clotting time was rechecked at 37°C. by a modified Lee and White[7] technic, and the blood clotted as a poor gel only after 16 hours. The capillary fragility test was strongly positive, and the bleeding time (Duke[8] method) was 14 minutes. Later, this puncture wound bled spontaneously for several hours. Blood smears showed numerous platelets present. The prothrombin clotting time (Quick[9] procedure) was prolonged to 42 seconds, with a 14-second control, and it was noted that the fibrin clot was a poor film. Because of the prolonged prothrombin clotting time, 60 mg. of vitamin K was given intravenously at 8:00 a.m. At 8:30 a clotting time showed the blood to be incoagulable; after standing for 24 hours no clot formed. A transfusion of 1000 cc. of whole blood was given, and at 11:00 a.m., the determination of the clotting time was repeated. A poor gel formed in 15 minutes, but it was not a good blood clot and another 1000 cc. of blood was administered. The patient at this time was bleeding freely from the gums, and the bleeding-time puncture wounds were also bleeding spontaneously. Vaginal staining began, and the patient lapsed into a semicomatose state. Meanwhile further studies on the blood specimens taken at 6:00 and 8:00 a.m. revealed that the addition of thrombin did not cause the blood to clot. It became apparent that there was complete absence of fibrinogen in the patient's blood, and a supply of Fraction I (Cohn)¶ was obtained. (Fraction I contains the

*From the Medical and Obstetrical Services, St. Elizabeth's Hospital.
†Visiting physician, St. Elizabeth's Hospital.
‡Assistant in surgery, St. Elizabeth's Hospital.
§Visiting obstetrician, St. Elizabeth's Hospital.

¶The Fraction I of normal human blood plasma used in this case was processed by the American National Red Cross from blood that it collected from voluntary donors. This material was prepared with the collaboration of the Department of Physical Chemistry, Harvard Medical School, and was furnished for civilian use without charge.

bulk of the fibrinogen of normal human plasma and a globulin active in reducing the clotting time in hemophilia.[10]) The fibrinogen content of the total plasma was roughly estimated for the patient, and 4.80 gm. of Fraction I (24 vials) dissolved in distilled water was given rapidly intravenously by syringe. The clotting time at 2:30 p.m. was 5 minutes, and the bleeding time was 5 minutes. The patient's general condition had deteriorated; she was stuporous and vomited brownish fluid. Another 1000 cc. of blood was started, and a sterile vaginal examination was attempted but the patient began to flow profusely from below. She was quickly prepared, and at 4:00 p.m. a rapid cesarean section was performed. The uterus was plum colored and infiltrated with blood, and it was removed by a rapid hysterectomy. The surgeons and observers agreed that after the removal of the uterus bleeding seemed to cease; subsequently no further bleeding from the gums or into the skin was noted.

After the operation the patient developed a moderate degree of shock; the blood pressure was 60/40, and the pulse 160. After a transfusion of 1000 cc. of whole blood she rallied; at 7:00 p.m. the clotting time was less than 1 minute and the bleeding time was normal. At 8:00 a.m. on February 2, the patient voided and her general condition was fairly good. The clotting time was 1 minute; no abnormal bleeding was noted but because of a low hematocrit (22 per cent) a transfusion of 1000 cc. of blood was given.

The subsequent course was uneventful, the bleeding and clotting times were within normal limits, and although the patient was literally "black and blue" from head to foot, she dangled her legs on February 3, was out of bed on February 5 and was discharged on February 12. She was rechecked periodically for several months after this episode, and all blood studies were within normal limits.

Autopsy on the infant revealed a macerated fetus with no special findings. The uterus and placenta were studied by Dr. Arthur Hertig, who reported the following pathological findings:

> Examination shows a slightly premature placenta. Probable intrauterine death is evidenced by fibrosis of villi. There is premature separation of the toxic type, and moth-eaten degeneration of trophoblasts. Hemorrhage into decidua is noted. The uterus is of the couvelaire type.
>
> Owing to marked post-mortem changes, the amount of syncytial degeneration is impossible to evaluate. There is no atheromatosis of decidual sinusoids.

Unfortunately the uterus, after its removal, was placed in formalin solution for about 10 minutes. Subsequently studies on extracts of the organ (by Dr. O. W. Smith) failed to reveal any evidence of fibrinolytic activity, but it was believed that the formalin may have destroyed the labile fibrinolysin.

The most important blood specimens were those obtained at 6:00 a.m. and 8:00 a.m. on February 1, before the administration of blood and fibrinogen. Since only small amounts of these oxalated and clotted blood specimens were available, experiments were limited. The immediate problem was to determine the cause of incoagulability of the blood and this was investigated, insofar as possible, by a study of each of the various clotting factors.

There was no evidence in either clinical or laboratory studies of liver damage in this patient. Although rare, hypoprothrombinemia has been reported in the absence of obstructive jaundice and liver disease, in this case the prolonged prothrombin clotting time suggested the possible diagnosis of hypoprothrombinemia. However, the fibrin clot formed during the test was so scanty that the lack of fibrinogen was suspected. The addition of thrombin to the blood and plasma specimens obtained at 8:00 a.m. failed to produce coagulation, and this finding, in the light of subsequent observations, proved that the lack of fibrinogen was the cause of the clotting defect.

Addition of calcium to blood and plasma of this patient did not restore coagulability; consequently lack of calcium was readily ruled out.

No evidence of an anticoagulant was found in the patient's blood. Direct addition of pretransfusion whole blood and plasma to normal blood and plasma caused no inhibition of clotting.

Addition of potent bovine thrombin to pretransfusion specimens of the patient's whole blood and plasma did not cause coagulation. Subsequently, fibrinogen determinations carried out on oxalated pretransfusion specimens revealed a complete absence of fibrinogen. Specimens obtained during the evening following operation showed a fibrinogen level of 0.5 gm. per 100 cc., and specimens obtained three days postoperatively gave a fibrinogen value of 0.35 gm. per 100 cc. It seems unquestionable that the incoagulability of the patient's blood was due to a complete lack of fibrinogen.

Afibrinogenemia is a rare disease that has been reported as a congenital defect and in severe liver disorders.[11, 12] Neither of these causes could be established in this case. In view of the recent work of the Smiths[4-6, 13-15] and the studies of other investigators on fibrinolysin, the explanation for the lack of fibrinogen and of fibrin in this patient seemed to rest most logically on the presence of a fibrinogenolysin or a fibrinolysin.

Observations on the small clot formed in the blood specimen obtained at 6 a.m. after standing overnight showed that the clot, although small, had not lysed. For several days after delivery, experiments were carried out on the pretransfusion *serum* specimens to demonstrate the presence of a fibrinolysin, but no lysis of clots formed from fibrinogen (Fraction I) and normal plasma was observed. However, experiments on the pretransfusion *plasma* (kept in a deep freeze) indicated that when fibrinogen (Fraction I) was added to this plasma and allowed to stand at 37°C. overnight, no clotting occurred on the addition of thrombin to the mixture. On the other hand, when normal human plasma was used as the source of fibrinogen, a clot occurred when thrombin was added. This observation seemed to indicate that there was a protective antifibrinogenolysin in the normal plasma and suggested that the lack or destruction of *antifibrinogenolysin* was the cause of the afibrinogenemia in this patient.

Discussion

It seems well established that the cause of the *coagulation defect* was the complete lack of fibrinogen. The occurrence of acquired afibrinogenemia is extremely rare, especially in the absence of liver disease. Dieckmann,[2] in 1936, reported that in 5 of 11 cases of abruptio placentae extremely low fibrinogen levels were found; after delivery fibrinogen returned to normal. In one case Dieckmann[2] states that "the blood failed to clot in the test tube" and this patient "bled from the gums, stomach, uterus and into subcutaneous tissues." No detailed studies on the clotting mechanism were carried out in Dieckmann's cases, and he attributed the clotting defect to a lowering of the fibrinogen content due to blood loss and the mobilization of fibrin at the site of placental separation.

In 1946 Tagnon and his associates[16] described, in a paper on fibrinolysis, a patient with incoagulable blood after a post-partum hemorrhage. Fibrinogen added to the patient's plasma, which had been collected shortly before death, clotted, but the clot dissolved within an hour. This group of investigators postulate that shock, especially that associated with hemorrhage and burns, results in anoxia with a release of a tissue factor that may have a precipitating effect on the production of fibrinolysin. However, in the case reported above, the patient was not in shock when her blood was first found to be incoagulable; moreover, fibrinolytic activity in the blood has been described in a variety of conditions unassociated with shock.

It must be admitted that the present knowledge of fibrinogenolysis and fibrinolysis is in a confused and uncertain state. MacFarlane[17] states that

"plasminogen of normal blood is of a potential activity to destroy the total fibrinogen of normal blood in a few minutes." Plasmin is held in an inert form by an antifibrinolysin, antiplasmin. Plasmin can be activated by a variety of conditions, which either destroy antiplasmin or activate plasminogen. MacFarlane[17] indicates that the mechanism of plasmin activation is obscure, and he states that it may be concerned with shock, tissue breakdown, blood coagulation and other phenomena.

Smith[5] recently discovered in menstrual fluid a euglobulin that is both a vascular toxin and a fibrinolysin. Moreover, he extracted from the serum of toxemic and other patients a euglobulin with fibrinolytic activity similar to that found in menstrual discharge. In the hypothesis advanced, the source of the fibrinolytic factor is in the degenerating decidua, and the Smiths[4] state that this tissue substance is akin to Menkin's "necrosin." Whether this fibrinolysin (or fibrinogenolysin) is a proteolytic enzyme released directly from tissue itself or whether there is an activation of fibrinolysin or an inhibition of antifibrinolysin remains to be determined. In any event, the work of the Smiths offers a new and promising approach to the problem of the etiology of toxemia of pregnancy, and it has shed light on the obscure and difficult subject of fibrinolysis in general.

It is apparent that the coagulative defect is not the whole story in this hemorrhagic diathesis. In the case reported above, there was severe vascular damage associated with spontaneous bleeding from mucous membranes and into the skin without evidence of thrombocytopenia. It has long been claimed that the toxin in toxemia of pregnancy acts on the blood vessels.[18] The Smiths[4] also state that the toxin from the decidua is a vascular toxin as well as a proteolytic enzyme. As suggested by Williams[19] twenty-five years ago, there is a striking analogy between the activity of this type of toxin and certain snake venoms having toxic vascular and proteolytic effects.

From a practical standpoint, if similar cases are encountered, administration of large amounts of fibrinogen (as Fraction I, Cohn), to restore the coagulability of the blood and the rapid removal of the uterus with its presumably toxic contents, may be, as it seemed in the case reported above, a life-saving procedure.

Summary and Conclusions

A case of hemorrhagic diathesis in pregnancy with separation of the placenta is described. The patient had none of the usual manifestations of toxemia of pregnancy but had a bleeding disorder characterized by spontaneous bleeding from the gums and into subcutaneous tissues and incoagulability of the blood.

Studies on the blood revealed a total lack of fibrinogen as the cause of the clotting defect.

Administration of a large amount of fibrinogen (Fraction I, Cohn) intravenously was followed by a return of the clotting time to normal, and removal of the uterus was accomplished, with recovery of the patient.

Suggestive evidence of a lack of an antifibrinogenolysin was noted in experiments carried out on the plasma of the patient. However, a definite fibrinolytic effect was not established in the serum, plasma or whole blood. The failure to demonstrate a fibrinolysin may have been due to technical difficulties and does not necessarily rule out the presence of this factor.

The concept of a toxin arising in the decidua capable of exerting a toxic effect on the blood vessels, as well as having a proteolytic activity, gains support in some measure from the findings in this case.

We are indebted to Drs. O. W. Smith, G. V. S. Smith and L. K. Diamond for their advice and help.

References

1. DeLee, J. B. Case of fatal hemorrhagic diathesis, with premature detachment of placenta. *Am. J. Obst.* **44**:785-797, 1901.
2. Dieckmann, W. J. Blood chemistry and renal function in abruptio placentae. *Am. J. Obst. & Gynec.* **31**:734-745, 1936.
3. Kellogg, F. S. Toxemias of pregnancy. *Clinics* **4**:585-647, 1945.
4. Smith, G. V., and Smith, O. W. Late pregnancy toxemia. I. Review of experimental findings. *West. J. Surg. Obst. & Gynec.* **55**:288-294, 1947.
5. Smith, O. W. Menstrual toxin. I. Experimental studies. *Am. J. Obst. & Gynec.* **54**:201-211, 1947.
6. Smith, G. V. S. Menstrual toxin. II. Clinical significance. *Am. J. Obst. & Gynec.* **54**:212-218, 1947.
7. Lee, R. I., and White, P. D. Clinical study of coagulation time of blood. *Am. J. M. Sc.* **145**:494-503, 1913.
8. Duke, W. W. Pathogenesis of purpura hemorrhagica with special reference to part played by blood platelets. *Arch. Int. Med.* **10**:445-469, 1912.
9. Quick, A. J. Clinical application of hippuric acid and prothrombin tests. *Am. J. Clin. Path.* **10**:222-233, 1940.
10. Edsall, J. T., Ferry, R. M., and Armstrong, S. N. Chemical, clinical and immunological studies on products of human plasma fractionation. *J. Clin. Investigation* **23**:557-565, 1944.
11. Quick, A. J. *The Hemorrhagic Diseases and the Physiology of Hemostasis.* 340 pp. Springfield, Ill.: Charles C Thomas, 1942.
12. Heindl, I. A., Anderson, B. G., and Friedlander, R. I. Acute idiopathic hypoprothrombinemia, response to massive doses of vitamin K. *Ann. Int. Med.* **29**:347-356, 1948.
13. MacFarlane, R. G., and Pilling, J. Observations on fibrinolysis: plasminogen, plasmin and antiplasmin content of human blood. *Lancet* **2**:562-565, 1946.
14. MacFarlane, R. G., and Biggs, R. Observations on fibrinolysis: spontaneous activity associated with surgical operations, trauma, &c. *Lancet* **2**:862-864, 1946.
15. Willson, J. R., and Munnell, E. R. Fibrinolytic activity in blood serum during pregnancy complicated by hypertensive toxemias. *Proc. Soc. Exper. Biol. & Med.* **62**:277-279, 1946.
16. Tagnon, H. J., Levenson, S. M., Davidson, C. S., and Taylor, F. H. L. Occurrence of fibrinolysis in shock, with observations on prothrombin time and plasma fibrinogen during hemorrhagic shock. *Am. J. M. Sc.* **211**:88-96, 1946.
17. MacFarlane, R. G., and Biggs, R. Fibrinolysis: its mechanism and significance. *Blood* **3**:1167-1187, 1948.
18. Willson, P. Uteroplacental apoplexy (haemorrhagic infarction of uterus) in accidental haemorrhage. *Surg., Gynec. & Obst.* **34**:57-78, 1922.
19. Williams. Cited by Willson.[18]

NITRATE METHEMOGLOBINEMIA

HAROLD MARCUS, M.D.,* AND JOY R. JOFFE, M.D.†

BROOKLYN AND NEW YORK CITY

MORE than forty years have passed since the first report of a fatal case of methemoglobinemia secondary to bismuth subnitrate ingestion.[1] Fifteen years ago Roe[2] reviewed the subject and reemphasized the hazards attending its use. Nevertheless, during the past four years 3 more cases have been reported.[3-5] A recent experience with a newborn infant has prompted us to review the general subject of nitrate methemoglobinemia, with emphasis on the causes, the types encountered, the mechanism involved and the rationale of present-day therapy.

Thirty cases of methemoglobinemia secondary to bismuth subnitrate, ammonium nitrate and nitrates in well water have been reported. The case reported below followed the ingestion of bismuth subnitrate on prescription.

We wish to point out that 4 of the 5 fatal cases of nitrate methemoglobinemia were in the group that followed bismuth subnitrate administration. Hence it is our opinion that still another warning to the medical profession regarding its use is indicated, particularly in view of the rapidly favorable outcome following the application of accepted therapeutic procedures.

CLASSIFICATION OF METHEMOGLOBINEMIAS

Methemoglobinemia may occur during the course of various diseases or may follow the ingestion of a variety of toxic agents. A slight modification of Ferrant's[6] classification is as follows:

Plasma methemoglobinemia. In this variety the methemoglobin is formed in the plasma after the liberation of hemoglobin from the red blood cells by hemolysis. This may occur in blackwater fever, eclampsia, paroxysmal hemoglobinuria, anaerobic sepsis and Winckel's disease of the newborn.

Cellular methemoglobinemia. In this variety hemoglobin, which contains iron in its ferrous form, is oxidized within the red blood cell by various agents to methemoglobin, which contains iron in its ferric form. This type is further subdivided into: idiopathic or enterogenous — according to van den Bergh,[7] nitrite is formed in the bowel from nitrate by nitrite-forming organisms, and absorption is encouraged by a damaged intestinal mucosa — and toxic, which comprises the largest and most important group of methemoglobinemias (the agents responsible include primarily the drugs containing nitro and amino groups, such as derivatives of aniline, certain sulfonamides, nitrates and nitrites[8-10]).

Our interest centers on the methemoglobinemias produced by nitrate ingestion.

REVIEW OF THE LITERATURE

According to Beck,[11] cases of bismuth subnitrate poisoning were reported as early as 1793, but impurities such as arsenic were thought to be responsible. Eusterman and Keith[12] cite Gamgee[13] as the first to demonstrate in 1886 that amyl nitrite could produce methemoglobinemia. In 1906 Bennecke and Hoffmann[1] reported the first fatal case of methemoglobinemia following bismuth subnitrate ingestion. Shortly afterward, Böhme[14] presented a report of a fatal case of methemoglobinemia following the administration of bismuth subnitrate by enema. He believed that intestinal putrefaction accelerated nitrite formation and rapid poisoning and stated that in fatal cases patients invariably suffered from intestinal disease. Thus, the danger of administration of bismuth subnitrate to infants, particularly when intestinal dysfunction existed, was established over forty years ago. Nowak and Gütig[15] showed that adults were not immune to nitrite poisoning after bismuth subnitrate. In reviewing the literature, Beck,[11] in 1909, made the first concise contribution on the general subject of poisoning due to nitrate, though limiting himself to bismuth subnitrate.

Years later, Eusterman and Keith[12] reported 2 nonfatal cases of methemoglobinemia in adults following the administration of ammonium nitrate as a diuretic. In both cases there was evidence of intestinal dysfunction. Tarr[16] collected 9 cases of methemoglobinemia following the ingestion of ammonium nitrate, of which he personally observed 4. In his cases renal impairment rather than intestinal dysfunction was the common denominator.

Roe,[2] in 1933, reported the fourth case of methemoglobinemia due to bismuth subnitrate ingestion and recommended the use of bismuth subcarbonate in its place for the treatment of diarrhea.

In the past few years a series of papers on methemoglobinemia due to the ingestion of well water of high nitrate content have appeared. Schwartz and Rector[17] reported a case of idiopathic methemoglobinemia in an infant fed a powdered milk formula and living in the country. Comley,[18] in describing 2 cases of this type, clarified the above

*Assistant physician, Maimonides Hospital, Israel Zion Division; assistant physician, Jewish Sanatorium and Hospital for Chronic Diseases; formerly, resident in medicine, Meadowbrook Hospital, Hempstead, New York.

†Assistant resident, Chest Service, Bellevue Hospital; formerly, resident in medicine, Meadowbrook Hospital, Meadowbrook, New York.

syndrome and attributed the methemoglobinemia to the nitrates in well water. Additional cases were reported from Belgium by Ferrant,[6] again from country communities in the United States by Faucett and Miller,[19] Chapin[20] and Stafford[21] and from Canada by Medovy, Guest and Victor.[22]

Case Report

D. B., a 3-week-old infant with a birth weight of 4 lb., 9 oz., was discharged from the hospital on the 9th day on an Olac formula. At the age of 2 weeks he had attained a weight of 5 lb., 12 oz. Six days prior to admission diarrhea developed, and a change of formula was made. The diarrhea persisted, however, and bismuth subnitrate was administered in a compound prescription at the rate of 0.1 gm. (1½ gr.) every 3 or 4 hours. Medication was taken as ordered for 1 day but was withheld on the night prior to admission because of the patient's bluish color. On the following morning the color improved, and medication was resumed. That evening cyanosis became marked. The attending physician administered physiologic saline solution by hypodermoclysis and referred the patient to the hospital.

Physical examination revealed a grayish-blue cyanosis. The weight was 5 lb., 8 oz. The temperature was 98°F. Activity was normal, and there was no evidence of dehydration. The head and neck were essentially normal. The heart did not appear enlarged; its rate and rhythm were normal, and no murmurs were audible. The lungs were clear to percussion and ascultation. Except for phimosis the remainder of the examination was negative.

Urinalysis and a complete blood count were within normal limits. The blood was chocolate brown when the first specimen was drawn.

The admission diagnosis of methemoglobinemia was established after the initial withdrawal of blood for examination, though the etiology was not determined until the following day. Premature management was begun at once, and the infant was given a small blood transfusion and kept in an atmosphere of high oxygen concentration. Because respiratory difficulty was not marked, methylene blue therapy was withheld initially. This course was justified by the rapid improvement incident to the measures employed. Residual cyanosis was barely visible twelve hours after admission, and twenty-four hours after admission it had disappeared completely.

Present Concepts

Formation of Methemoglobin

Van den Bergh,[7] writing on enterogenous cyanosis, stated that nitrates were converted into nitrite within the intestinal tract by bacteria, the nitrite being absorbed through the injured intestinal wall and recovered in the blood stream. Years later ZoBell[23] showed that many organisms found in the intestinal tract could change nitrate into nitrite in vitro. It is now generally hypothesized that, after the introduction of nitrate into the intestinal tract, there is normally a conversion of a portion of the nitrate into nitrite and ammonia. After absorption in greater or lesser amount, nitrite may react with hemoglobin or may be excreted by the kidney. The reaction of nitrite with hemoglobin results in the formation of methemoglobin by oxidation, ferrous ion being converted to ferric ion. The process is reversible, but reconversion to hemoglobin is slow, requiring a minimum of eight or nine hours, according to Wendel,[24] and longer according to other authors. Inasmuch as anoxia is the basis of the symptomatology, the crux of the problem lies in the management of the patient during the first eight to twelve hours.

Before cyanosis due to methemoglobinemia occurs, a considerable amount of nitrite must be absorbed and retained in contact with hemoglobin. According to Wendel,[8] methemoglobin should make up at least 10 per cent of the total blood pigment before cyanosis becomes visible. Miller[4] quotes 3 gm. of methemoglobin per 100 cc. of blood as the critical figure for visible cyanosis.

Our review of the literature has uncovered many factors that play a part in the absorption of nitrite and its reaction with hemoglobin to form methemoglobin.

Chemical nature of the toxic agent. It is generally recognized that methemoglobinemia appears more quickly after nitrate ingestion than after sulfanilamide or plasmochin.[8]

Age of patient. Infants are more susceptible because of the greater frequency of gastrointestinal disturbances, the presence of a bacterial flora more favorable to nitrite production (Böhme,[14]) the existence of nitrate-splitting organisms high in the intestinal tract, which would facilitate the reduction of the nitrate to nitrites before the nitrate could be completely absorbed,[25] and possibly because of less renal efficiency in eliminating nitrites.

Mode of administration of nitrate. It has long been recognized that a more severe and prompt methemoglobinemia results from the rectal administration of nitrate (Böhme[14]).

Integrity of intestinal mucosa. Van den Bergh[7] implicated the injured intestinal mucosa as a factor many years ago.

Amount of nitrate administered. The appearance of cyanosis due to methemoglobinemia is generally dependent on the amount of nitrate ingested. This was recognized by [illegible]e[14] years ago, and substantiated by the case[illegible] Barker and O'Hare[26] and Tarr.[16]

Renal status. Nitrite retention on the basis of renal insufficiency has been implicated by Tarr.[16]

Rapidity of passage through the intestinal tract. Incomplete reduction of nitrate to ammonia may be the result of rapid passage through the intestine with the intermediate nitrite present in greater quantity near the absorbing surface of the intestine.

pH of blood. Greenberg et al.[27] have shown that the conversion of hemoglobin to methemoglobin in the presence of nitrite occurs more rapidly in an acid medium. Furthermore, Marshall and Marshall[28] lessened the symptoms of nitrite poisoning experimentally by intravenous administration of sodium carbonate or bicarbonate.

Diagnosis of Methemoglobinemia

The diagnosis of methemoglobinemia with scientific certainty is made only by spectroscope or spectrograph. The average physician, however, will rely on the following points to establish a diagnosis

of nitrate methemoglobinemia: if no history of nitrate ingestion is obtainable, it is incumbent on the physician to ascertain whether or not well water of high nitrate content has been ingested; the cyanosis is described as an unusual grayish-brown color; the blood in methemoglobinemia is generally described as chocolate brown, brownish red or brownish black (hemolysis does not occur); blood transfusion frequently intensifies the cyanosis by enhancing the formation of additional methemoglobin; and chemical analysis of blood demonstrates nitrites.

Therapeutic Rationale

A certain percentage of patients with minimal cyanosis and symptoms will recover without therapy after withdrawal of the toxic agent. Wallace,[5] however, likens the methemoglobinemia following nitrate ingestion to the effects of rapid hemorrhage and that of enterogenous cyanosis and aniline poisoning to the effects of slow blood loss. The most urgent therapy is therefore required in cases of more advanced nitrate methemoglobinemia, and the critical period is the first twelve hours.

The treatment of choice in severe cases is the use of an agent that will hasten reconversion of methemoglobin to hemoglobin. Thionin and methylene blue are two such agents. Ascorbic acid and niacin possess the same property but act more slowly. Hence, they are more applicable to cases of methemoglobinemia due to aniline, sulfanilamide and plasmochin. Methylene blue catalyzes the physiologic reduction of methemoglobin by the body. According to Wendel,[8, 24] after administration in dilute solution, methylene blue is converted to the leuko or reduced form of dye by certain cellular enzymes in the red blood cell and other body cells. According to Hauschild,[29] who reported on the effectiveness of thionin and methylene blue (tetramethyl thionin hydrochloride) in the treatment of methemoglobinemia, a reversible oxidation-reduction system of thionin-leukothionin is produced initially. The hemoglobin-methemoglobin system is then shifted in favor of hemoglobin. Hauschild claimed that thionin administered intravenously was effective in ten minutes. Lederer[30] is quoted by Ferrant[6] as follows: "Thionin, a non-toxic, violet dye, not methemoglobin formative, has a reducing power five times that of methylene blue." Thus, the use of thionin in place of methylene blue bears investigation.

At present a rapid though brief action may be expected after the intravenous injection of methylene blue. The accepted dosage is 1 or 2 mg. per kilogram of body weight injected intravenously over a period of five minutes. An effect can be expected within thirty minutes. Injection of the dye under the skin and around the vein is painful and may produce necrosis. Furthermore, too rapid injection may produce hives and severe burning of the mouth. It must be emphasized again that the dye when used intravenously produces a rapid but brief action. Hence, it is important to supplement with oral therapy for prolonged action. Ten times the intravenous dose should be given orally at the same time and repeated once or twice to cover the critical period of anoxia. It has, moreover, been suggested that glucose in vitro transforms methemoglobin into oxyhemoglobin. We have also mentioned the favorable influence of an alkaline medium. Hence, the utilization of glucose and sixth-molar lactate solutions after the intravenous administration of methylene blue appears to be desirable.

Summary

The general subject of nitrate methemoglobinemia is reviewed.

A case of bismuth subnitrate methemoglobinemia recently encountered is presented.

The mechanisms involved in the formation of methemoglobin and in the evolution of rational therapy are discussed.

The increasing number of reports of methemoglobinemia due to nitrates in well water point to the growing importance of this variety.

It is re-emphasized that the use of bismuth subnitrate as a therapeutic agent is unnecessary, unwarranted and hazardous.

References

1. Hoffmann. Discussion of Bennecke. Fall von Wismutvergiftung in folge stomachaler Verabreichung von Bismutum subnitricum bei einem 3 Wochen alten Kinde. *München. med. Wchnschr.* **53**:945, 1906.
2. Roe, H. E. Methemoglobinemia following administration of bismuth subnitrate: report of fatal case. *J. A. M. A.* **101**:352-354, 1933.
3. Miller, R. C. Methemoglobinemia occurring in case of chronic ulcerative colitis. *Proc. Staff Meet., Mayo Clin.* **19**:308-311, 1944.
4. Miller, G. E. Bismuth subnitrate poisoning with methemoglobinemia: report of case in diabetic. *Gastroenterology* **4**:430-434, 1945.
5. Wallace, W. M. Methemoglobinemia in infant as result of administration of bismuth subnitrate. *J. A. M. A.* **133**:1280, 1947.
6. Ferrant, M. Methemoglobinemia: two cases in newborn infants caused by nitrates in well water. *J. Pediat.* **29**:585-592, 1946.
7. van den Bergh, A. A. H. Enterogene Cyanose. *Deutsches Arch. f. klin. Med.* **83**:86-106, 1905.
8. Wendel, W. B. Methemoglobinemia: significance and treatment. *Memphis M. J.* **14**:3-5, 1939.
9. Willi, H. Methämoglobinbildung und Innenkörperanämie durch Anastil. *Ann. Paediat.* **159**:282, 1942.
10. Gough, W., and Ashton, N. Methaemoglobinaemia after ingestion of anti-gas ointment. *Brit. M. J.* **2**:854, 1944.
11. Beck, E. G. Toxic effects from bismuth subnitrate: with reports of cases to date. *J. A. M. A.* **52**:14-18, 1909.
12. Eusterman, G. B., and Keith, N. M. Transient methemoglobinemia following administration of ammonium nitrate. *M. Clin. North America* **12**:1489-1496, 1929.
13. Gamgee, A. Cited by Eusterman and Keith.[12]
14. Böhme, A. Über Nitritvergiftung nach interner Darreichung von Bismuthum subnitricum. *Arch. f. exper. Path. u. Pharmakol.* **57**:441-452, 1907.
15. Nowak, J., and Gütig, C. Nitritvergiftung durch Bismutum subnitricum. *Berl. klin. Wchnschr.* **45**:1764-1768, 1908.
16. Tarr, L. Transient methemoglobinemia due to ammonium nitrate. *Arch. Int. Med.* **51**:38-44, 1933.
17. Schwartz, A. S., and Rector, E. J. Methemoglobinemia of unknown origin in two week old infant. *Am. J. Dis. Child.* **60**:652-659, 1940.
18. Comley, H. H. Cyanosis in infants caused by nitrates in well water. *J. A. M. A.* **129**:112-116, 1945.
19. Faucett, R. L., and Miller, H. C. Methemoglobinemia occurring in infants fed milk diluted with well water of high nitrate content. *J. Pediat.* **29**:593-596, 1946.
20. Chapin, F. J. Methemoglobinemia from nitrates in well water. *J. Michigan State M. Soc.* **46**:938, 1947.
21. Stafford, G. E. Methemoglobinemia in infants from water containing high concentrations of nitrates. *Nebraska State M. J.* **32**:392-394, 1947.
22. Medovy, H., Guest, W. C., and Victor, M. Cyanosis in infants in rural areas (well-water methaemoglobinemia). *Canad. M. A. J.* **56**:505-508, 1947.

23. ZoBell, C. E. Factors influencing reduction of nitrates and nitrites by bacteria in semisolid media. *J. Bact.* **24**:273-281, 1932.

24. Wendel, W. B. Control of methemoglobinemia with methylene blue. *J. Clin. Investigation* **18**:179-185, 1939.

25. Cornblath, M., and Hartmann, A. F. Methemoglobinemia in young infants. *J. Pediat.* **33**:421-425, 1948.

26. Barker, N. M., and O'Hare, J. P. Use of salyrgan in edema. *J. A. M. A.* **91**:2060-2064, 1928.

27. Greenberg, L. A., Lester, D., and Haggard, H. W. Reaction of hemoglobin with nitrite. *J. Biol. Chem.* **151**:665-673, 1943.

28. Marshall, W., and Marshall, C. R. Action of nitrites on blood. *J. Biol. Chem.* **158**:187-208, 1945.

29. Hauschild, F. Die Wirkung des Katalysins (Thionin) bei der Methämoglobinvergiftung. *Arch. f. exper. Path. u. Pharmakol.* **184**:458-467, 1937.

30. Lederer, J. A. Contribution à l'étude pharmacodynamique de la thionine: action sur la métabolisme des hydrates de carbone et toxicité. *Arch. internat. de pharmacodyn. et de thérap.* **55**:347-361, 1937.

STREPTOMYCIN IN THE TREATMENT OF SALMONELLA ENTERITIS IN INFANTS*

SIDNEY ROSS, M.D.,† FREDERIC G. BURKE, M.D.,‡ E. CLARENCE RICE, M.D.,§
HAROLD BISCHOFF, M.D.,¶ AND JOHN A. WASHINGTON, M.D.||

WASHINGTON, D. C.

THE susceptibility of various strains of salmonella in vitro to streptomycin has been adequately demonstrated by West et al.[1] However, the clinical efficacy of this antibiotic in salmonella enteritis has not been too extensively investigated, and relatively few cases have been reported thus far among children. Seligmann et al.[2] used streptomycin in 5 cases of enteritis due to *Salmonella typhimurium* in the newborn period and observed only a transitory sterilization of the bowel, and in all 5 cases the pathogenic organism reappeared in the stool, usually within forty-eight hours after the drug had been discontinued. A relatively small oral dose of streptomycin was used in Seligmann's series, ranging between 0.2 and 0.8 gm. a day for three or four days. In 1 case, combined oral and intramuscular administration was used and similarly failed to effect a permanent cure. Swiller and his associates,[3] on the other hand, reported a bacteriologic cure of an eight-month-old salmonella carrier when 1 gm. of streptomycin was given orally daily for twenty consecutive days. Pulaski and Amspacher[4] treated 3 cases of salmonella enteritis in infants, using a daily oral dose of 100 mg. per kilogram of body weight for four to seven days, and the stool cultures became negative and remained so during a three-week follow-up period. Except for these three reports, the literature on the treatment of salmonella enteritis in infancy with streptomycin has been limited.

During the past year, we have had the opportunity of treating 8 patients, ranging in age from three months to three years, with large doses of streptomycin for a prolonged interval. This report deals with the clinical and bacteriologic observations made in these cases.

TABLE 1. *Summary of 8 Cases of Salmonella Enteritis Treated with Streptomycin.*

CASE NO.	AGE	ETIOLOGIC ORGANISM	STREPTOMYCIN SENSITIVITY BEFORE TREATMENT	STREPTOMYCIN SENSITIVITY AFTER RELAPSE	DOSE OF STREPTOMYCIN	
					ORAL	INTRAMUSCULAR
	mo.		*unit/cc.*	*unit/cc.*		
1	15	*S. manhattan*	5.0	5.0	0.4 gm. every 4 hr. for 7 days; 0.8 gm. every 4 hr. for 8 days.	None
2	3	*S. typhimurium*	5.0	5.0	0.4 gm. every 4 hr.	None
3	36	*S. oranienberg*	10.0	10.0	0.6 gm. every 3 hr.	0.1 gm. every 6 hr.
4	5	*S. typhimurium*	4.0	5.0	0.1 gm. every 4 hr.	None
5	4	*S. anatis*	12.5	—*	0.4 gm. every 4 hr.	0.1 gm. every 6 hr.
6	9	*S. meunchen*	10.0	7.5	0.4 gm. every 4 hr.	0.1 gm. every 6 hr.
7	1	*S. oranienberg*	10.0	12.5	0.4 gm. every 4 hr.	0.15 gm. every 8 hr.
8	8	*S. typhimurium*	6.0	7.5	0.6 gm. every 4 hr.	0.2 gm. every 8 hr.

*No relapse.

*From the Research Foundation of Children's Hospital.
This study was supported by a grant from the Antibiotic Study Section of the Division of Research Grants and Fellowships, the National Institutes of Health, United States Public Health Service.

†Instructor in pediatrics, George Washington University School of Medicine; research fellow, National Institute of Health; junior attending physician, Children's Hospital.

‡Associate clinical professor, Georgetown University School of Medicine; associate clinical professor, George Washington University School of Medicine; director of pediatric instruction, Children's Hospital.

§Pathologist, Children's Hospital.

¶Research fellow, National Institutes of Health; resident, Children's Hospital.

||Assistant clinical professor, George Washington University School of Medicine; attending pediatrician, Children's Hospital, Walter Reed General Hospital and Episcopal Eye, Ear and Throat Hospital.

Bacteriology

Rectal swabs were obtained daily and immediately streaked by the bedside on salmonella-shigella (SS) agar and desoxycholate citrate (DC) and incubated for twenty-four hours. In addition, Kauffmann's tetrathionate broth was seeded with the rectal swab and subcultured on SS plates after eighteen to twenty-four hours of incubation. Colorless colonies from SS and DC mediums were subcultured into Kligler's iron agar and identification of the organisms was performed with the use of type-specific H serums.* In questionable cultures, sugar broths, examination for motility, indole formation and other biochemical identification procedures were employed. The distribution of the various types of salmonella in this series was as follows: *S. typhimurium*, 3 cases; *S. oranienberg*, 2 cases; and *S. meunchen*, *S. manhattan* and *S. anatis*, 1 case each.

It is worth while to emphasize the desirability of repeated stool-culture examinations both for diagnosis and for follow-up purposes even with the selective mediums now available. The latter permit the detection of a small number of pathogens in feces by substantially inhibiting the coliform group. However, unless repeated stool examinations are performed during and after treatment with streptomycin, abortive "cures" may be reported.

Hydroxyamine hydrochloride (1:300), adjusted to a pH of 6.0, was incorporated in some control SS plates in an attempt to neutralize the inhibitory effect of the streptomycin excreted in the stool. However, the plates showed definite overgrowth with *Escherichia coli*, indicating a vitiating effect of hydroxyamine hydrochloride on the coliform inhibitory properties of the mediums itself, and this procedure was therefore abandoned.

It is well to point out that tetrathionate broth proved to be the most sensitive medium in the isolation of salmonella organisms in our 8 cases. A total of 160 stool cultures were obtained in this series (an average of 20 per patient), of which 78 were positive for salmonella. Of these, 73 specimens yielded salmonella in tetrathionate broth, 42 on desoxycholate citrate agar, and 39 on SS agar. In the majority of cultures, the organism was recovered from two or all three mediums simultaneously. In 33 out of 78 positive cultures, however, salmonella was isolated from only one culture medium. Tetrathionate broth exclusively yielded a positive culture in 28 cases, whereas positive cultures were isolated solely on SS agar in 3 specimens and desoxycholate citrate in 2. This serves to emphasize the desirability of culturing stools on all three mediums simultaneously, in view of the fact that no single medium yielded salmonella on *all* positive stool specimens. If only one medium is to be seeded at the bedside for follow-up purposes in cases of proved salmonella infection, tetrathionate broth would undoubtedly be the most useful one to use.

Table 1 (*Continued*).

Case No.	Duration of Treatment	Total Dose of Streptomycin		Outcome	Comment
	days	oral *gm.*	intramuscular *gm.*		
1	15	57.6	None	Recurrence	Stool cultures positive throughout streptomycin therapy
2	12	30.4	None	Recurrence	Stool cultures negative during therapy; recurrence of positive cultures 6 days after streptomycin discontinued.
3	11	37.2	4.1	Recurrence	Stool cultures negative during therapy; recurrence of positive culture 8 days after streptomycin discontinued.
4	8	4.8	None	Recurrence	Stool cultures negative during therapy; recurrence of positive culture 5 days after streptomycin discontinued.
5	10	24	4	Cure	Stool cultures negative during therapy; still negative after 1 mo. follow-up study.
6	14	33.6	5.6	Recurrence	Stool cultures negative during therapy; recurrence of positive culture 3 days after streptomycin discontinued.
7	11	26.4	4.9	Recurrence	Stool cultures negative during therapy; recurrence of positive culture 5 days after streptomycin discontinued.
8	14	50.4	8.4	Recurrence	Majority of stool cultures positive during streptomycin therapy

Dosage and Mode of Administration of Streptomycin

The lack of response of salmonella infections to smaller doses of streptomycin in Seligmann's series prompted us to use a considerably larger dosage ranging from 0.8 to 4.8 gm. a day orally, with an average of 2.4 gm. daily. The drug† was administered for an interval ranging between eight and

*We are indebted to Dr. Erich Seligmann, of the National Salmonella Typing Center, New York, and to Drs. H. Carlquist and L. R. Kuhn, of the Army Medical Center, Washington, D. C., for confirmation and final identification of the organism by the use of group-specific O serums.

†Kindly supplied as syrup of streptomycin (50 mg. per cubic centimeter) by E. R. Squibb and Sons. This preparation was readily accepted and well tolerated by all the patients.

fifteen days, with an average of eleven and three-fifths days per patient. Each patient received an average of 28 gm. of streptomycin orally during the course of therapy. In spite of these large doses, spot blood assays during treatment showed no detectable level of the drug when the oral mode of administration was used exclusively. This is in keeping with the well known fact that streptomycin is not absorbed from the intestinal tract. In 5 of the 8 cases in our series, streptomycin was simultaneously administered intramuscularly in a dose ranging between 0.4 and 0.6 gm. a day.

Results

The pertinent data on the eight cases are presented in Table 1. It will be noted that only 1 patient in this series (Case 6) showed salmonella to be permanently absent from the stool cultures. This infant received both oral and intramuscular streptomycin. In 6 other cases a definite inhibitory effect on both the salmonella organisms and the normal stool flora was observed during the period of drug administration; however, in spite of the large doses used, the pathogen reappeared in the stool three to eight days after discontinuation of the drug. In Case 1, in which the strain proved to be *S. manhattan*, the patient continued to have positive stool cultures throughout the course of therapy, even when 4.8 gm. of streptomycin a day was administered orally. In 4 of the 5 patients who received combined oral and intramuscular streptomycin, there did not appear to be any enhancement in the efficacy of therapy or any noticeable delay in the reappearance of the salmonella organisms. It thus appeared that combined oral and parenteral administration of streptomycin was no more effective than oral administration alone. In view of the small number of cases in this series, it was not possible to say whether any particular strain of salmonella showed any significant variation in response to streptomycin therapy. None seemed to be apparent except perhaps for the undue bacteriologic refractoriness of the patient with the manhattan strain of salmonella.

It is to be noted that the streptomycin sensitivities observed in this series ranged from 4.0 to 12.5 microgm. per cubic centimeter prior to institution of streptomycin therapy. Of interest was the observation that in no case was any significant increase in streptomycin resistance noted when the pathogen reappeared in the stools after termination of therapy. Thus, the failure of streptomycin in salmonella enteritis can hardly be explained on the basis of acquired resistance of the organism. Nor can it be explained on the basis of the initial resistance of salmonella since a sensitivity of 4.0 to 12.5 microgm. per cubic centimeter would place the salmonella among the relatively sensitive groups of organisms susceptible to streptomycin. Experimental studies on streptomycin stool levels obtained after the administration of varying doses of the drug orally to infants have been conducted in our laboratory during the past several months, and it has been found that with doses ranging from 0.2 to 0.4 gm. every four hours, the streptomycin stool levels ranged between 10,000 and 20,000 microgm. per gram of dried feces. To a first approximation, this was the dosage used in the present series of salmonella enteritis. Thus, the sensitivity of the salmonella organisms in these 8 cases was exceeded 1000 to 5000 times in streptomycin stool concentration, and yet streptomycin therapy was singularly disappointing. An analogous situation obtains in typhoid fever, in which streptomycin has been demonstrated to produce a marked inhibitory action against *Eberthella typhosa* in vitro and yet clinically and bacteriologically the antibiotic exerts no salutary effect against typhoid fever in human beings.

All 8 children showed an uneventful clinical improvement and were discharged from the hospital in good condition. Whether any favorable clinical effect was exerted by streptomycin on the course of the disease in this series is problematic. Only 3 of the 8 cases showed any marked constitutional symptoms at the time of admission, characterized by high fever, toxicity, acidosis and dehydration. It is not unlikely that vigorous management of these symptoms per se was the significant factor in effecting a favorable outcome.

Summary

Eight cases of salmonella enteritis in infants and children were treated with streptomycin in large doses. Three of the patients received the drug orally alone, whereas the other 5 were given the antibiotic both orally and intramuscularly.

In spite of the demonstrated susceptibility of the salmonella organism to streptomycin in each case, only 1 of the 8 patients was rendered permanently free of salmonella. In the other 7, an inhibitory effect on both the salmonella organisms and the normal stool flora was observed during the period of drug administration; however, three to eight days after streptomycin had been discontinued, the pathogen reappeared in the stools. No significant increase in streptomycin resistance was noted in any case.

We are indebted to Miss Sara Stevens, Mrs. Eleanor Weinstein and Miss Susan Gougé for their technical assistance.

References

1. West, M. G., Doll, S. R., and Edwards, P. R. Inhibition of *Salmonella* cultures by streptomycin. *Proc. Soc. Exper. Biol. & Med.* **60**:363, 1945.
2. Seligmann, E., Barash, L., and Cohlan, S. Q. Streptomycin treatment of salmonella enteritis in infants. *J. Pediat.* **30**:182-187, 1947.
3. Swiller, H. E., Swiller, A. I., and Traub, F. B. Salmonella carrier treated successfully with streptomycin. *Pediat.* **31**:474, 1947.
4. Pulaski, E. J., and Amspacher, W. H. Streptomycin therapy for certain infections of intestinal origin. *New Eng. J. Med.* **237**:419-428, 1947.

MEDICAL PROGRESS

SURGERY IN CHRONIC ARTHRITIS

JOHN G. KUHNS, M.D.*

BOSTON

SURGERY is employed in chronic arthritis primarily to remove or to decrease deformities and disabilities that have occurred within and about the joints.[1] If adequate early medical and orthopedic care is given, almost all disability can be prevented in chronic arthritis, and much later surgery can be avoided.[2] If the joints that show swelling, muscular spasm and pain are splinted to relieve muscular spasm, in a position as near to full extension as they can comfortably be placed, and if flexion deformity is then prevented by a part-time maintenance of this position, little deformity will develop. Weakness in the supporting musculature must be prevented by exercise and other physiotherapy. Severe crippling is usually found in the patient when these simple measures have been neglected.[3]

In the preceding decade attempts were made through surgical measures to cure the arthritis or to alter certain physiologic disturbances. Among the surgical measures sympathectomy[4] for the lower extremity and parathryoidectomy[5] were most widely discussed. For the most part the early discussions of these procedures were optimistic, but later reports were more critical and disappointing.[6, 7] Old measures were discarded and forgotten, and new ones were enthusiastically accepted every year.[8] One procedure that is still vigorously defended[9] — and as strongly condemned as valueless[10] — is the extensive removal of so-called foci of infection. This subject was recently reviewed by Freyberg,[11] who concluded that if the arthritis was infectious a localized infection might be a trigger mechanism that started it. Removal of foci of infection was probably of no value in rheumatoid arthritis of long duration. Foci of infection should be attacked only as part of a broad program of treatment.

The aims of surgery in chronic arthritis are outlined by Wilson.[12] He speaks of the value of partial rehabilitation through well thought out surgical procedures followed by prolonged physiotherapy. In a similar manner Fisher[13] states that orthopedic surgery can often prevent deformity in chronic arthritis, can correct deformity sometimes, can always improve function and can alleviate pain.

No surgical measures should be undertaken unless there is reasonable assurance that they will decrease pain or improve function. The usual indications and contraindications were outlined succinctly fifteen years ago by Wilson and Osgood.[14] The indications and contraindications need little modification: quiescence of the arthritis, optimal general condition and good morale of the patient, adequate facilities for hospitalization and follow-up care. The patient should be emotionally stable and co-operative, with a sincere desire to get well. In most cases the operation is but one step in the restoration of articular function; rarely is function restored by the operative procedure alone. Before operation there should be several weeks of muscular re-education or at least muscle-setting exercises to teach the patient to use, as well as to strengthen, the muscles that will later move the joint or the limb.[15] Operative procedures are usually valueless unless there is sufficient muscular strength obtainable to make useful function possible later. After operation a prolonged period of physiotherapy and exercises is required to get the greatest possible benefit. The surgeon should have a definite plan of rehabilitation. Usually, deformities in the upper extremity are treated before those in the lower extremity.

Surgical procedures are generally not contemplated in the treatment of chronic arthritis until one has clinical and laboratory evidence that the disease is quiescent.[16] Most surgeons state that the patients have a more rapid convalescence, with fewer complications, and that exacerbations in the arthritis are much less likely to occur if surgery is delayed until the disease has become quiescent.[17, 18] It has been suggested that surgical procedures may be performed more easily if one does not wait for complete healing and quiescence of the arthritis.[19] Although operation can be carried out with greater ease before bony anklyosis and severe contractures have occurred, if the disease is still active the convalescence is prolonged and a recrudescence of acute arthritis is often observed.[20] Moreover, after the inflammation in the joint subsides, a remarkable spontaneous improvement in function is sometimes seen. Unnecessarily radical procedures may be performed if one does not wait for the unaided recovery of function that follows quiescence of the disease. In rare cases operation is necessary in the early, acute stage of the arthritis, particularly when adduction deformity is present in both hips, to give the patient comfort or to make nursing care possible.[21]

*Instructor in orthopedic surgery, Harvard Medical School; lecturer in orthopedic surgery, Boston University School of Medicine; chief of surgical and orthopedic staffs, Robert Breck Brigham Hospital.

The avowed purposes of surgical treatment in chronic arthritis have been given as follows[22]: to make a diagnosis; to relieve pain; to correct or to improve a deformity; and to obtain motion in a stiff joint. Usually, diagnosis is certain long before operation is contemplated. When there are unusual features or if tuberculosis is suspected, examination of articular tissues[23] or occasionally of regional lymph nodes, may be of value.[24] Sometimes in monarticular arthritis when there is little change and no progression to other joints, arthrotomy with pathological examination of articular tissue may be necessary for the making of a diagnosis.[25]

Operations and other procedures to relieve pain are palliative only. They do not influence the course of the arthritis or improve the impaired function. Yet they are at times most welcome to the sufferer from constant pain in the joints. Such procedures consist chiefly of injections about major nerves or into the periarticular tissues about an affected joint.[26] Rarely are sensory nerves that supply the joint cut. Occasionally, the surgical stiffening of a painful joint is carried out, pain being relieved by the stopping of all motion.[27]

Most surgical treatment in chronic arthritis is carried out for the correction of deformities. Manipulations, lengthening of contracted soft tissues and osteotomies are the procedures that are most frequently employed.[28] Less than 5 per cent of the cases of rheumatoid arthritis progress to the ankylosis of joints; some degree of articular damage is the usual end result. The procedures available to improve motion in a stiffened joint are osteotomy, arthroplasty and resection.[29] Although the surgical indications for the correction of disabilities in both rheumatoid arthritis and osteoarthritis are similar, it is better for the sake of clarity to review them separately.

Rheumatoid Arthritis

Manipulation — the stretching of contracted soft tissues about a joint with the patient anesthetized — has been discussed frequently.[30] According to Lloyd Williams,[31] it is of value in quiescent disease to correct mild deformity and to increase motion by stretching or rupturing adhesions and by stretching shortened muscles and fascia. It should be employed with caution in quiescent disease. It may light up a quiescent inflammation.[32] Because the bones in chronic arthritis do not have normal strength and break easily, great care must be exercised in carrying out manipulations.[33] The usual technic is to bring the distal portion of the limb first into greater flexion and then to extend it slowly. If full correction is considered unwise at the first attempt, the manipulation can be repeated as soon as the soreness caused by the first manipulation has subsided. After manipulation the limb is held in the improved position for several days, and then physiotherapy is resumed.[34] If no correction follows one manipulation, further ones will be ineffective, and operative lengthening of the tight structures must usually be performed.[35]

When soft tissues are so tight that no improvement follows corrective casts or manipulation, two useful procedures have been described for the correction of contracted soft tissues. These can be employed most effectively at the knee, and less well at the elbow or finger joints. When major surgery is considered hazardous and when there is not a great amount of bony atrophy, the contracted tissues can be stretched safely by turnbuckles attached to Kirschner wire. The Kirschner wires are drilled through the bones on the proximal and distal sides of the joint. By turning of the turnbuckles the articular surfaces are distracted, and the contractures are slowly stretched.[36] The entire limb is usually kept in a posterior cast or in balanced traction for comfort. By this method relatively painless correction of flexion and of subluxation can be obtained in two or three weeks. This method cannot be used when the bones are extremely atrophied, for the wires will then be pushed through the bones. No pressure sores develop, nor is there extensive interfascial fibrosis, both of which are found with wedging casts and forcing apparatus. After correction has been obtained, the limb is put in a bivalved cast and physiotherapy is begun.

Immediate correction of resistant contractures in rheumatoid arthritis can be obtained by lengthening the tendons of the tight muscles and by freeing the posterior portion of the articular capsule if the general condition of the patient permits a major surgical procedure.[37] A number of technics have been described since the early description of Silver.[38] The simplest and most effective is that described by Wilson.[39] The essential features of this operation are cutting of the iliotibial band and fascia lata, lengthening of the biceps femoris tendon and freeing of the posterior portion of the articular capsule. The leg is held in full extension until healing is well advanced, when active exercises are given. Walking with support is permitted in two or three weeks. When full, immediate motion of the flexion deformity stretches the popliteal vessel too much, extension is carried out gradually with changes of casts at weekly intervals. In this way there is no circulatory embarrassment in the foot, and no injury occurs to the common peroneal nerve. When the motion in the knee joint is quite limited, with considerable articular destruction, rotation osteotomy performed just above the condyles of the femur has been advocated.[40] The disadvantage of this procedure is that much stiffness develops in the muscles and fascia while the osteotomy is healing, before movement can again be started in the knee.[41]

At the elbow joint a permanent flexion deformity can be improved by lengthening the expansions of the biceps tendon.[42] The flexion deformity at the elbow is usually not a serious disability, and operation is not often required. In the fingers, freeing the

volar side of the capsule at the interphalangeal joints permits full extension at these joints.[43] At the hip, when flexion is present, section of the fascia lata in the upper third of the thigh is occasionally useful.

In the popliteal space and occasionally at the sides of the interphalangeal joints an outpouching or herniation of a part of the articular capsule may appear. Such swellings are usually herniations of the joint, which at the knee are sometimes called Baker's cysts.[44] Occasionally these swellings subside spontaneously or decrease with pressure dressings. If they persist or become larger, their removal is indicated. It has been suggested that some of them may be enlarged bursas at the back of the knee.[45] The treatment usually advocated is simple removal of the sac, with overlapping of the fascia or muscles across the origin of the herniation from the articular capsule. Similarly, rheumatic nodules, which appear on the extensor surface of the bones in about 20 per cent of patients with rheumatoid arthritis, sometimes become irritated and painful. When pressure comes continually upon such an area, the rheumatic nodule should be removed.

When there is persistent painful swelling of the articular capsule from excessive formation of synovial fluid, aspiration and the application of a pressure dressing are usually advised. Opinion is divided about the value of repeated aspirations either for diagnosis or for therapy.[46] Usually, only temporary relief is given. Continued hydrarthrosis at a joint is generally evidence of chronic irritation within the articular cavity.[47] If clinical or x-ray examination shows any internal derangement, a foreign body, a displaced meniscus or greatly thickened synovial tissue, an arthrotomy with the removal of the tissue causing the irritation is indicated. The articular capsule is opened through the front or back of the joint, depending upon the position of the irritating material. After removal, the hydrarthrosis usually ceases.

Synovectomy — the removal of a portion or all of the synovial membrane — still has no established indications in rheumatoid arthritis.[48] Its value has been recognized since its early description by Swett.[49] The synovial membrane is no longer removed under the mistaken idea that it may be a focus of infection. The chief indication in rheumatoid arthritis is mechanical interference with function.[50] If the swelling and thickening of the synovial membrane have been present less than a year, treatment with deep x-ray therapy may cause them to subside.[51] In massive swelling that is resistant to x-ray therapy or has been present for a long time synovectomy is generally required. The usual technic is to remove the synovial membrane as completely as possible through a long parapatellar incision. No tourniquet is used, but hemostasis is controlled with the electrocautery.[52] Degenerated semilunar cartilages and interarticular ligaments must usually be removed also at the knee joint. Partial synovectomy is sometimes required at the elbow joint when the thickened tissue interferes with extension. Removal of the synovial membrane on both sides of the olecranon and from the olecranon fossa is usually adequate. Adhesions form quickly after synovectomy if motion cannot be started soon and usually account for most of the poor results.[53] Cellophane and thin nylon membrane have been used over the suprapatellar space with some benefit to prevent adhesions after synovectomy.[54] Where there is great destruction of the articular cartilages in addition to the thickened synovial membrane, synovectomy is usually not helpful; arthroplasty or arthrodesis is generally advocated.

Osteotomy — the cutting of a bone to provide a better position for function — is indicated occasionally in the treatment of arthritis.[55] When a joint is stiff the surgeon must decide whether function will be served better by the formation of a new joint or by leaving the joint stiff, with the limb placed in the best position for function. At the wrist and finger joints, and usually at the tarsal joints, a stiff joint in a good position is considered to be the most satisfactory procedure. When the wrist joint has been destroyed, osteotomy is advocated followed by fusion in about 30° of dorsiflexion. At the interphalangeal joints when the joint is ankylosed or seriously deformed, osteotomy is carried out through the joint. After osteotomy the joint is held in 30 to 40° of flexion with fine Kirschner wire until the joint becomes solidly fused.[56] This gives a much more useful finger than an arthroplasty, which always causes lateral instability at the interphalangeal joints. Osteotomy has been mentioned at the metacarpophalangeal joint to correct severe subluxation and ulnar deviation. Here the distal end of the metacarpal bone is trimmed off squarely. Occasionally the proximal end of the proximal phalanx must be also reshaped.[43] Resection of the outer part of the acromion — "acromioplasty" — has been advocated to lessen pain and improve motion at the limited arthritic shoulder joint.[19] Improved motion and lessening of pain at this joint have been reported.

During the past few years attempts have been made to correct the fixed anterior bowing of the spine by osteotomy.[57] Osteotomy is performed in the lumbar spine to improve the position of the dorsal and cervical regions of the spine in anterior flexion. This is a very common late deformity in rheumatoid spondylitis. Osteotomy is usually performed through the pedicles and articular facets in the lumbar region. The lumbar spine is then hyperextended, and a surgical fusion is performed to hold the lumbar spine permanently in this position.[58] Several varying surgical technics have been reported.[59]

Arthrodesis, the operative fusion of a joint in a useful position, is rarely employed in the treatment of rheumatoid arthritis. When a joint is severely damaged the natural tendency of the disease is to heal the lesion with fibrous or bony ankylosis of the

joint. When this ankylosis is unsound, arthrobesis may be indicated.[60] But most patients prefer either the use of apparatus to avoid pain or an operative procedure that will leave them with motion at the joint.[61, 62] Arthrodesis is justified as a temporary expedient to relieve pain rapidly at the knee or hip joint. This is performed by the use of nails or wire driven across the joint. Such immobilizing material can later be removed, and an operation to obtain motion can be performed when the arthritis becomes quiescent. In many cases, after arthrodesis, more arthritis and sprain have been observed in the joints above and below the arthrodesis. In the foot, arthrodesis of the tarsal joints and of the ankle joint in the best position for walking are useful procedures when these joints are hopelessly damaged and cause pain.[63] Usually, nature fuses these joints in the course of the arthritis and the surgeon's task is to keep the foot in good weight-bearing position until fusion takes place. For deformities in the anterior portion of the foot the procedures used for the treatment of severe static deformities are advocated.

Arthroplasty — the formation of a new, movable joint after anklyosis from rheumatoid arthritis — has been called the essence of patchwork surgery. Well fitting articular surfaces can be formed without difficulty in the major joints, but the bones frequently do not remain as they had been shaped.[64] The osteoporotic bones and the atrophied muscles, which are frequently found in the later stages of rheumatoid arthritis, are poor materials to work with. With weight bearing and with motion the ends of the bones often become greatly distorted. This distortion is much less when plastic or metallic molds are fitted over the articular surfaces.[65] Orthopedic procedures have been reported in most of the major joints, but useful joints, after arthroplasty, have been reported chiefly at the elbow, the hip and the knee.

At the elbow joint a number of procedures have been described from wide resection to arthroplastic procedures. All these procedures usually give a movable elbow joint, but an arthroplasty gives a somewhat more stable elbow.[66] Usually, fascia lata is interposed between the bone ends. A wide range of painless motion is reported, but normal strength and stability are not regained. At the knee joint, fascia has also been used as an interposition material to prevent reankylosis after arthroplasty. In most cases this has worn away quickly, but a small number of good results have been reported.[67] Cellophane and nylon membrane have been employed in a few cases, with somewhat greater success.[21] In most cases a limited range of motion has been obtained after prolonged physiotherapy. Samson[68] believes that arthroplasty of the knee should be performed only rarely in rheumatoid arthritis.

At the hip joint when ankylosis has taken place arthroplasty is indicated when the patient must sit for work. In persons who must stand, a stiff, painless hip in a good position for weight bearing is usually more satisfactory. Some satisfactory arthroplasties were obtained by the use of fat or fascia as interposition materials, but in most cases these substances quickly degenerated under pressure and reankylosis occurred.[69] Metallic or plastic cups that fit over the femoral head have withstood distortion and have given much more useful hip joints.[70]

Arthroplasties have been reported on practically all the major joints of the body. A number of operations on the fingers and toes have been described. But for the most part, except for the elbow, the hip and the knee, these offer little gain in function. Rarely is arthroplasty required at the temporomandibular joint; ankylosis here is rare but some limitation of motion is common.[71] A number of successful arthroplasties on this joint have been reported.

Osteoarthritis

Osteoarthritis rarely produces serious deformity, and, consequently, does not require surgical treatment very often. However, in persons who do heavy labor and in others with some malformation in a weight-bearing joint, severe pain and deformity are sometimes seen with osteoarthritis. Operation is performed more often for the relief of pain than for any other reason in osteoarthritis. Although most persons who seek surgical treatment are past middle age they stand surgical procedures surprisingly well. The indications and prerequisites are the same as those for rheumatoid arthritis.[12] Whereas there is no active inflammatory process or quiescence of the disease in osteoarthritis, any inflammation from mechanical insult should have subsided before operation is undertaken. More surgical procedures are performed for disability at the hip and knee than for any other joints.

Manipulation under anesthesia is performed in osteoarthritis for the joints of the cervical spine, the shoulder, the hip, the knee and the foot. It has been suggested that impingement and irritation of cervical nerves can be relieved at times by gentle manipulation of the cervical spine. Osteoarthritis of the shoulder is frequently associated with fascial and capsular irritation and subsequent adhesions. These can be released, and freer and less painful motion may result. Mennell[30] has demonstrated that improved motion may follow manipulation of the hip in osteoarthritis if there is not much deformity of the femoral head. Sometimes, repeated gentle manipulations remove almost all disability. Manipulation is rarely required at the knee. If there is much limitation of extension it is usually the result of an internal derangement, and arthrotomy is often required.[72] A rigid valgus deformity of the foot is occasionally seen in osteoarthritis. Manipulation and fixation in a corrected position in a plaster cast, with later a support to the foot, often relieve this.

Neurectomy

Cutting of the obturator nerve has been said to relieve most of the pain in osteoarthritis of the hip joint. The sensory distribution to the hip joint is extensive, but most of the anterior distribution comes from the obturator nerve.[73] This is cut within the pelvis just before the nerve enters the obturator foramen. Sometimes, for completeness, fibers coming to the posterior capsule with the nerves to the external rotators of the hip are also cut. This operation, which is not a serious surgical procedure, is usually reserved for elderly persons in whom relief of pain, rather than improvement in function, is the chief desideratum. Denervation has been reported in other joints, but here it has as yet not passed the experimental stage.

When there is much limitation of motion from osteoarthritis in early middle age, various plastic procedures have been described to remove the bony overgrowth and to improve motion. Cheilotomy gives relief until the re-formation of overgrowth again limits motion about the joint. Partial cheilotomy and acetabuloplasty[74] give temporary relief only. At the hip, arthroplasty[75] is useful in monoarticular disease (so-called secondary osteoarthritis in younger persons). At the knee a partial synovectomy and trimming of bony overgrowth have lessened pain and increased motion.[62, 76]

Removal of the patella when it was markedly overgrown and interfered with function was advocated by Berkheiser.[77] Subsequent reports have been conflicting,[78] but most recent reports and my own experience suggest that the patella is essential for the normal mechanics of extension at the knee.[79] Plastic procedures on the patella seem to give a better functional result than complete removal.

Degeneration of intra-articular ligaments and other structures about the joint in osteoarthritis are commonly found. At the shoulder partial or complete tears of the supraspinatus tendon are a frequent accompaniment. In the lower back, ruptures of the intervertebral disk are a not uncommon complication of osteoarthritis. Unless there is severe sciatic pain the diagnosis may be difficult. Operative removal of the extruded disk substance is sometimes required both in the cervical and in the lumbar spine. At the knee in osteoarthritis, internal derangement is often evidence of a foreign body or a displaced meniscus. Relief of pain and surprising recovery of function often follow arthrotomy.

At various times attempts have been made to improve the circulation about the joint with the mistaken idea that in this way a halt could be made in the degenerative process and that a regression in the periarticular overgrowth might result. One of the earliest means employed was forage,[80] a drilling into the bone to provide new channels for vascularization. This has been carried out at the hip joint more often than any other joint. Here drill holes were bored into the femoral neck. More recently, transplantation of available muscle, chiefly the vastus externus, has been made into the femoral neck to accomplish the same end.[81]

When there is much deformity from osteoarthritis at any joint a number of simple and helpful procedures have been reported to correct such a deformity.[82] One of these is osteotomy. Although this procedure has been used on rare occasion at the acromioclavicular joint, the elbow joint and the wrist, it has been employed most extensively at the hip joint. The operation that has received the most attention has been the intertrochanteric osteotomy of McMurray.[83] This procedure is not particularly shocking. By it, adduction and external rotation of the leg can be fully corrected, and the femoral shaft can be displaced inward, changing the weight thrust a little and making for increased stability of the joint. Such procedures are usual y reserved for patients in later middle life when correction of deformity is desired rather than increase in articular motion.[84]

In the elderly patient many surgeons recommend complete stiffening of the painful joint for the relief of pain. One of the simple, earlier methods for obtaining this end was simple nailing of the hip through the neck into the acetabulum.[85] It was found that many hips with osteoarthritis failed to become ankylosed by this means. A number of more extensive procedures, some of them carried out in two stages, have been reported.[86]

References

1. Osgood, R. B. Orthopedic treatment of rheumatism. In *Survey of Chronic Rheumatic Diseases.* 338 pp. London: Oxford University Press, 1938.
2. Balensweig, I. What can orthopedics offer arthritic? *M. Clin. North America* **30**:635-644, 1946.
3. Kuhns, J. G. Management of chronic arthritis. *West Virginia M. J.* **39**:44-51, 1943.
4. Adson, A. E., and Rowntree, L. G. Surgical indications for sympathetic ganglionectomy and trunk resection in treatment of chronic arthritis. *Surg., Gynec. & Obst.* **50**:204-215, 1930.
5. Leriche, R. L'avenir et la signification de la chirurgie des parathyroïdes. *Presse méd.* **40**:1133-1136, 1932.
6. Key, J. A. Treatment of chronic arthritis. *West. J. Surg.* **52**:385-398, 1944.
7. Mandl, F. Development of parathyroidectomy during last fifteen years. *J. Internat. Coll. Surgeons* **3**:297-309, 1940.
8. Hipps, H. E. New surgical procedure in acute infectious arthritis: preliminary report. *Texas State J. Med.* **34**:276-284, 1938.
9. Wyatt, B. L., and Bensema, C. E. Relationship of urological tract and skin to chronic arthritis. *Urol. & Cutan. Rev.* **46**:113-116, 1942.
10. Davidson, L. S. P. Aetiology and treatment of rheumatoid arthritis. *Glasgow M. J.* **140**:2-5 (December), 1943.
11. Freyberg, R. H. "Focal infection" in relation to rheumatic diseases: critical appraisal. *J. Am. Dent. A.* **33**:1101-1108, 1946.
12. Wilson, P. D. Surgical reconstruction of arthritic cripple. *M. Clin. North America* **21**:1623-1639, 1937.
13. Fisher, A. G. T. Orthopaedic and surgical aspects of chronic rheumatism. *Practitioner* **143**:286-296, 1939.
14. Wilson, P. D., and Osgood, R. B. Reconstructive surgery in chronic arthritis. *New Eng. J. Med.* **209**:117-125, 1933.
15. Comroe, B. I. Physical therapy in rheumatoid arthritis. *Arch. Phys. Med.* **26**:677-682, 1945.
16. Lewin, P. Stabilization — arthrodesis — arthroplasty of knee joint. *S. Clin. North America* **18**:65-83, 1938.
17. Fisher, A. G. T. Orthopedic and surgical treatment in rheumatoid type of arthritis. In *Rheumatic Diseases.* Edited by L. E. Hill and P. Ellman. 270 pp. Baltimore: William Wood & Co., 1938.
18. Bastow, J. Some orthopaedic procedures employed in treatment of arthritis. *Proc. Roy. Soc. Med.* **35**:80-86, 1942.
19. Smith-Petersen, M. N., Aufranc, O. E., and Larson, C. B. Useful surgical procedures for rheumatoid arthritis involving joints of upper extremity. *Arch. Surg.* **46**:764-770, 1943.
20. Joplin, R. J., and Baer, G. J. Treatment of arthritic joints. *J. A. M. A.* **18**:937-944, 1942.

21. Kuhns, J. G., and Potter, T. A. Orthopaedic care of arthritis. In *Comroe's Arthritis.* Third edition. Philadephia: Lea & Febiger, 1949.
22. Kuhns, J. G. Operations and surgical procedures. In Steinbrocker, O. *Arthritis in Modern Practice: The diagnosis and management of rheumatoid and allied conditions.* 606 pp. Philadelphia: W. B. Saunders Co., 1941. Pp. 536-554.
23. Webster, R. Studies in tuberculosis: biopsy study of lymphatic glands in diagnosis of tuberculous disease of joints. *M. J. Australia* **1**:160-166, 1942.
24. Gellman, M. Regional glandular biopsy in diagnosis of bone and joint tuberculosis. *Bull. School Med. Univ. Maryland* **25**:135-149, 1941.
25. Kuhns, J. G. Chronic monarticular arthritis. *New Eng. J. Med.* **232**:128-132, 1945.
26. Steinbrocker, O. Local injections and regional analgesia with procaine solutions for intractable pain in chronic arthritis and related conditions. *Ann. Int. Med.* **12**:1917-1939, 1939.
27. Jones, E. Orthopedic treatment of chronic arthritis. *California & West. Med.* **43**:125-128, 1935.
28. Tippett, G. O. Orthopaedic surgery in treatment of rheumatism and rheumatoid arthritis. *Practitioner* **139**:271-278, 1937.
29. Platt, H. Surgery in chronic arthritis. In *A Survey of Chronic Rheumatic Diseases.* 338 pp. London: Oxford Univ. Press, 1938.
30. Mennell, J. *The Science and Art of Joint Manipulation.* Vol. 1. *The Extremities.* 233 pp. Philadelphia: Blakiston Co., 1939.
31. Lloyd Williams, I. H. On manipulation of joints. *J. Roy. Army M. Corps* **74**:86-91, 1940.
32. Douthwaite, A. H. Discussion on manipulative procedures in rheumatic disorders. *Proc. Roy. Soc. Med.* **32**:273-275, 1938.
33. Baer, G. J. Fractures in chronic arthritis. *Ann. Rheumat. Dis.* **2**: 269-273, 1941.
34. Forrester-Brown, M. Place of forcible manipulation in treatment of joints. *Brit. J. Phys. Med.* **4**:53-58, 1941.
35. Swaim, L. T., and Kuhns, J. G. Prevention of deformities in chronic arthritis. III. Lower extremity. *J. A. M. A.* **94**:1743-1745, 1930.
36. Badgley, C. Surgical treatment of chronic arthritis. In *Regional Orthopaedic Surgery and Fundamental Orthopaedic Problems.* Edited by J. E. M. Thomson. 265 pp. Ann Arbor: Edwards Bros., 1948.
37. Kuhns, J. G. Treatment of arthritis contractures of knee. *New Eng. J. Med.* **227**:975-980, 1942.
38. Silver, D. Rôle of capsule in joint contractures: with especial reference to subperiosteal separation. *J. Bone & Joint Surg.* **9**:96-105, 1927.
39. Wilson, P. D. Posterior capsuloplasty in certain flexion contractures of knee. *J. Bone & Joint Surg.* **11**:40-58, 1929.
40. Briggs, H. Flange osteotomy for correction of knees ankylosed in flexion. *J. Bone & Joint Surg.* **20**:374-378, 1938.
41. Fisher, A. G. T. Principles of orthopaedic and surgical treatment in rheumatoid type of arthritis. *J. Bone & Joint Surg.* **18**:657-666, 1937.
42. Wilson, P. D. Capsulotomy for relief of flexion contractures of elbow following fracture. *J. Bone & Joint Surg.* **26**:71-86, 1944.
43. Kuhns, J. G. Recovery of function in hand in chronic arthritis. *J. Bone & Joint Surg.* **17**:939-944, 1935.
44. Haggart, G. E. Posterior hernia of knee joint: cause of internal derangement of knee. *J. Bone & Joint Surg.* **20**:363-373, 1938.
45. Wilson, P. D., Eyre-Brook, A. L., and Francis, J. D. Clinical and anatomical study of semimembranous bursa, in relation to popliteal cyst. *J. Bone & Joint Surg.* **20**:963-984, 1938.
46. Freund, E. Pathological significance of intra-articular pressure. *Edinburgh M. J.* **47**:192-203, 1940.
47. Mauck, H. P. War surgery and traumatic lesions: severe acute injuries of knee. *Am. J. Surg.* **56**:54-63, 1942.
48. Pardee, M. L. Synovectomy of knee joint: review of literature and presentation of cases. *J. Bone & Joint Surg.* **30**:908-914, 1948.
49. Swett, P. P. Synovectomy in chronic infectious arthritis. *J. Bone & Joint Surg.* **5**:110-121, 1923.
50. Speed, J. S. Synovectomy of knee joint. *J. A. M. A.* **83**:1814-1820, 1914.
51. Kuhns, J. G., and Morrison, L. B. Twelve years' experience in roentgenotherapy for chronic arthritis. *New Eng. J. Med.* **235**:399-405, 1946.
52. Magnusson, R. Total synovectomy of knee joint. *Acta orthop. Scandinav.* **11**:235-263, 1940.
53. Ghormley, R. K., and Cameron, D. M. End results of synovectomy of knee joint. *Am. J. Surg.* **53**:455-459, 1941.
54. Harley, G. H., and Breck, L. W. Cellophane in bone and joint surgery. *Am. J. Surg.* **68**:229-231, 1945.
55. Milch, H. *Osteotomy of the Long Bones.* 294 pp. Springfield, Ill.: Charles C Thomas, 1947.
56. Marble, H. Management of hand injuries. *J. Indust. Hyg. & Toxicol.* **26**:189-192, 1944.
57. La Chappelle, E. H. Osteotomy of lumbar spine for correction of kyphosis in case of ankylosing spondylarthritis. *J. Bone & Joint Surg.* **28**:851-858, 1946.
58. Smith-Petersen, M. N., Larson, C. B., and Aufranc, O. E. Osteotomy of spine for correction of flexion deformity in rheumatoid arthritis. *J. Bone & Joint Surg.* **27**:1-11, 1945.
59. Briggs, H., Keats, S., and Schlesinger, P. T. Wedge osteotomy of spine with bilateral intervertebral foraminotomy. *J. Bone & Joint Surg.* **29**:1075-1082, 1947.
60. Lambert, C. N., and Miller, L. F. Results of surgical treatment of tuberculosis of joints. *Illinois M. J.* **79**:330-334, 1941.
61. Hass, J. Functional arthroplasty. *J. Bone & Joint Surg.* **26**:297-306, 1944.
62. Dickson, F. D. Surgical treatment of arthritis. *Ann. Surg.* **113**:869-876, 1941.
63. Kuhns, J. G. Care of foot in chronic arthritis. *Rheumatism* **1**:6-9, 1939.
64. Pfeiffer, D. B., and Bach, T. F. Reconstructive surgery in chronic arthritis. *M. Clin. North America* **24**:1745-1753, 1940.
65. Blum, G. Experimental observations of use of absorbable and non-absorbable plastics in bone surgery. *Proc. Roy. Soc. Med.* **38**:169-171, 1945.
66. MacAusland, W. R. Arthroplasty of elbow. *New Eng. J. Med.* **236**: 97-99, 1947.
67. Speed, J. S., and Smith, H. Arthroplasty: review of past ten years. *Internat. Abstr. Surg.* **80**:224-230, 1940.
68. Samson, J. E. La traitement chirurgical de la polyarthrite chronique. *Union méd. du Canada* **74**:578-589, 1945.
69. Kleinberg, S. Arthroplasty in lower extremity. *Arch. Surg.* **34**:1072-1087, 1937.
70. Smith-Petersen, M. N. Arthroplasty of hip: new method. *J. Bone & Joint Surg.* **21**:269-288, 1939.
71. Bayles, T. B., and Russell, L. A. Temporomandibular joint in rheumatoid arthritis. *J. A. M. A.* **116**:2842-2845, 1941.
72. Hendry, A. M. Osteoarthritis as orthopaedic problem. *Practitioner* **155**:89-94, 1945.
73. Tavernier, L., and Godenat, C. *Traitement chirurgical de l'arthrite seche de la hanche.* 157 pp. Paris: Masson et Cie, 1940.
74. Smith-Petersen, M. N. Treatment of malum coxae senilis, old slipped upper femoral epiphysis, intrapelvic protrusion of acetabulum, and coxa plana by means of acetabuloplasty. *J. Bone & Joint Surg.* **18**: 869-880, 1936.
75. Harmon, P. H. Arthroplasty of hip for osteoarthritis utilizing foreign-body cups of plastic. *Surg. Gynec. & Obst.* **76**:347-365, 1943.
76. Haggart, G. E. Surgical treatment of degenerative arthritis of knee joint. *J. Bone & Joint Surg.* **22**:717-729, 1940.
77. Berkheiser, E. J. Excision of patella in arthritis of knee joint. *J. A. M. A.* **113**:2303-2308, 1939.
78. Young, H. H., and Regan, J. M. Total excision of patella for arthritis of knee. *Minnesota Med.* **28**:909-914, 1945.
79. Cohn, B. N. E. Total and partial patellectomy: experimental study. *Surg., Gynec. & Obst.* **79**:526-536, 1944.
80. Mackenzie, J. F. Osteo-arthritis of hip and knee: description of surgical treatment. *Brit. M. J.* **1**:306-308, 1936.
81. Venable, C. S., and Stuck, W. C. Muscle-flap transplant for relief of painful monarticular arthritis (aseptic necrosis of hip). *Tr. South S. A.* **57**:172-186, 1946.
82. Neligan, A. R. Management of osteoarthritis. *Brit. J. Phys. Med.* **8**:100-103, 1945.
83. McMurray, T. P. Osteo-arthritis of hip joint. *J. Bone & Joint Surg.* **21**::1-11, 1939.
84. Kuhns, J. G. Orthopaedic treatment of hypertrophic arthritis of hip. *J. Bone & Joint Surg.*, **24**:547-554, 1942.
85. Jones, R. W. Arthrodesis of osteoarthritic hip. *J. A. M. A.* **110**:278-280, 1938.
86. Haggart, G. E. Degenerative arthritis of hip joint treated by one or two stage arthrodesis with metal fixation (Watson-Jones). *J. A. M. A.* **128**:502-507, 1945.

Correction. In the article entitled "Intensive Chrysotherapy (with Lauron) in Rheumatoid Arthritis," by Friedman and Steinbrocker, which appeared in the March 10 issue of the *Journal*, the value "*microgm.*" in Table 4 on page 365 should be changed to "*mg.*" throughout.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35151

PRESENTATION OF CASE

A seventy-year-old farmer was admitted to the hospital because of a very productive cough.

For several years he had a chronic cough, most severe in the morning, when he raised moderate amounts of whitish sputum. He was in otherwise good health for his age. Five months before admission the cough increased in frequency and productivity, so that at the time of admission he was raising about half a cupful of yellowish and occasionally blood-stained sputum each day. Progressive lack of appetite, weight loss and weakness appeared. A physician performed an x-ray examination eight days before entry. Penicillin therapy was given. The patient was told that he had a lung abscess that was increasing in size despite chemotherapy, and he was transferred here.

On admission he appeared weak and emaciated but in no acute distress. The tongue was red and smooth; he was edentulous, with an upper plate. The trachea was in the midline, and there were dullness to percussion and decreased breath sounds in the region of the right fourth rib posteriorly. There was no change in tactile fremitus. The heart was within normal limits. A small, indirect hernia was present in the right inguinal region. The prostate was twice the normal size but not hard. The blood pressure was 150 systolic, 90 diastolic.

The urine had a specific gravity of 1.026 and gave a + test for albumin. The white-cell count was 16,800, with 77 per cent neutrophils, 8 per cent lymphocytes, 8 per cent monocytes and 7 per cent eosinophils. The serum total protein was 6.06 gm. per 100 cc., chloride 105 milliequiv. per liter, and nonprotein nitrogen 24 mg. per 100 cc. The prothrombin time was 23 seconds (control, 16 seconds).

An electrocardiogram on the fifth hospital day showed a normal rhythm at a rate of 75, with the PR interval equal to 0.15 second and normal axis. The T waves were low upright in Leads 1, 2 and 3, with upright TV_2, V_4 and V_6 and flat T_{AVL} and low upright T_{AVF}.

X-ray examination of the chest showed an increased anteroposterior diameter. Both leaves of the diaphragm were low, and fluoroscopically were seen to be limited in their excursion. The lung fields were bright. In the apex of the right lower lobe lying posteriorly in contact with the chest wall was a rounded shadow, 7 cm. in diameter, in which there was a fluid level. The shadow was slightly lobulated in contour, and the upper portion of the wall of the cavity was seen to be irregular along its inner wall (Fig. 1). There was little or no reaction in the surrounding lung. The sputum was negative for acid-fast organisms, and cytologic examination for tumor cells was reported as "doubtful." Bronchoscopy demonstrated no abnormalities except that the dorsal division of the lower lobe was somewhat reddened, and a thin, whitish, mucoid secretion exuded from it. There was no fixation or deformity here

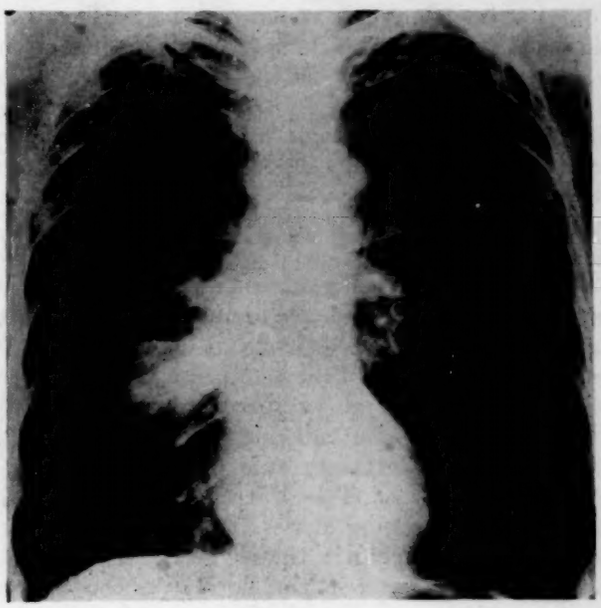

FIGURE 1.

or elsewhere. On the ninth hospital day a right lower lobectomy was performed. Toward the end of the operation the blood pressure fell to 90 to 100 systolic, 50 diastolic. At the end of the operation the blood pressure was up, and the condition was good. A blood transfusion of 2000 cc. was given.

Twelve hours later the patient's general condition seemed good, although there was a hypotension (blood pressure of 80 systolic, 40 diastolic), without rise in pulse. Fourteen hours after operation the blood pressure dropped to 60 systolic, 40 diastolic, and a marked bradycardia (rate of 44) appeared. An electrocardiogram showed an irregular auricular and ventricular rhythm, with auriculoventricular dissociation and prolonged QRS time. Many artifacts obscured the tracing, but the T wave in Lead 1 appeared upright, with a low upright T wave in Lead 2, inverted T wave in Lead 3 and depressed

ST segments in Leads CF_2 and CF_4, with probably upright T waves in Leads CF_2 and CF_4. He died thirty-six hours after the operation.

Differential Diagnosis

Dr. Lowrey F. Davenport: This is the recurrent problem of differential diagnosis between infection and tumor. Did this man have a simple lung abscess? Did he have an abscess that developed secondarily to bronchial obstruction, or was this a primary tumor in the lung with beginning central necrosis to account for the symptoms? I should like to see the x-ray films.

Dr. Stanley M. Wyman: The posteroanterior and lateral views show this well rounded, quite discrete shadow of increased density far posteriorly in the right chest and somewhat medially, and it seems to be close to the chest wall. There is a clearly defined fluid level within this round shadow. The wall of the shadow itself is thickened, and its inner contour is shaggy and irregular as the record states. This is a Bucky film taken for rib detail and shows the ribs and the spine in this area to appear within normal limits. The heart shadow is a little prominent in the region of the left ventricle, and the aorta is quite tortuous. The chest generally is emphysematous.

Dr. Davenport: We have to explain, then, a localized lung lesion in the dorsal portion of the right lower lobe. The differential diagnosis here is between infection and tumor. I believe, in a man of this age with this large an abscess cavity, who had a sputum negative for tubercle bacilli, that we can with reasonable certainty rule out the consideration of tuberculosis. The differential diagnosis lies between a simple lung abscess and an abscess that developed in a necrotic tumor mass. The localization of the abscess in the dorsal portion of the lower lobe is not uncommon for a simple lung abscess. However, we have nothing in the background of this patient to explain the appearance of lung abscess. Presumably his teeth had been removed many years previously, and there is nothing in the history as given to suggest any possible etiologic agent for a lung abscess. Lung abscesses as discrete as this usually show surrounding pneumonitis unless there has been intensive chemotherapy. Rarely in a lung abscess do we see such a sharply demarcated lesion as presented here. Most tumors arising in the bronchial tree in the periphery of the lung of a solitary nature, and of this size, are adenocarcinomas. In such a situation these tumors frequently outgrow their blood supply and show a central necrosis. A Papanicolaou stain on the material taken from the patient's sputum showed a doubtfully positive test. I assume that the material from this tumor was so necrotic that even though he was raising tumor cells, it might be difficult to recognize them under the microscope. The remaining findings at bronchoscopy are of no significance in a tumor situated as far posteriorly as this tumor was. We are given the symptom of chronic cough for several years. Apparently, that was the type of morning cough that a man who has spent seventy years of his life in New England is reasonably entitled to. The cough that became alarming and troublesome had been present for only five months. Cough of five months' duration is not unusual with a tumor such as this is, with a central necrosis. I would think, then, that the lung picture was that of a bronchiogenic tumor, probably an adenocarcinoma, undergoing central necrosis.

I think that secondarily it would be of some interest to try to puzzle out why he died within thirty-six hours of operation. When a patient dies within thirty-six hours of a major operation such as a lobectomy we should like to know, first, whether or not a suture had slipped following cough as he began to rouse from the anesthesia. However, with the drop in blood pressure the pulse did not become elevated. This bradycardia excludes the possibility of blood loss as explanation for the low blood pressure and symptoms twelve hours after operation. Over and over again we get confused between the differential diagnosis of pulmonary embolism and coronary occlusion. Pulmonary embolism may give a definite pattern of symptomatology. In a certain percentage of cases there are suggestive changes in the electrocardiogram. No changes diagnostic of pulmonary embolism were present in the second electrocardiogram, but the tracings suggest coronary occlusion. The secondary shock in a man of seventy who has arteriosclerosis of the coronary arteries may cause acute coronary occlusion. Whatever the trigger mechanism that precipitated the cardiac episode, a man who develops a sharp drop in blood pressure without evidence of blood loss, a cardiac rate of 42 and complete dissociation by electrocardiogram of auricular and ventricular rhythm must have a profound disturbance of cardiac conduction mechanism, presumably on the basis of coronary occlusion.

My final diagnosis is primary carcinoma of the bronchus and death thirty-six hours following operation from an acute coronary occlusion.

Dr. Donald S. King: Can you distinguish between abscess and tumor by the thickness of the wall and the shagginess of the wall?

Dr. Wyman: No, not in all cases. I think, as Dr. Davenport pointed out, that the thickness and contour of this wall together with the absence of the reaction about it, definitely favor tumor over an inflammatory process such as abscess. The two overlap, however, in certain cases and make it impossible to be certain.

Dr. Alfred Kranes: Knowing the tendency of these tumors to metastasize to the adrenal glands, could you consider acute adrenal insufficiency as a

possible mechanism for the hypotension following operation and the events that followed it?

Dr. Davenport: I do not think I would consider it as a probability. I might consider some such mechanism in the development of the low blood pressure, in the absence of anything else to explain it. We have no evidence of adrenal disorder prior to operation, and it seems hardly likely that he developed such a condition within thirty-six hours of operation.

Dr. Kranes: Except that this degree of surgery might be enough to throw a person into acute adrenal insufficiency. He had no previous sign of it, and I do not think that one can make the diagnosis. It is just speculation.

Dr. Edward B. Benedict: I think it is worth pointing out why we did a bronchoscopy on a tumor that was obviously quite peripheral and beyond the reach of the bronchoscope. We did it because sometimes we can find tumor cells in the bronchoscopic washings when we have negative cytologic findings in the sputum.

Dr. Benjamin Castleman: In this case a cytologic examination of the washings showed definite tumor cells. Then Dr. Soutter took over.

Dr. Lamar Soutter: There is one interesting point about the lack of surrounding pneumonitis. This patient had been on large doses of penicillin for a month prior to entry so that one could expect less pneumonitis than is usually found with an abscess. It might be questioned why anyone would do lung surgery on a patient of seventy who had emphysema. If he had had a benign abscess it could have been drained, which would have been a simpler procedure than a lobectomy. But because we believed that he had a malignant lesion and was going steadily downhill, we thought it reasonable to do a lobectomy on this man to rid him of his sepsis. This procedure for a peripheral tumor has a reasonable chance of effecting a cure and is much safer than a pneumonectomy in older patients. We believed that he would withstand such a procedure but not a pneumonectomy. He was seen by a cardiologist, who thought that the heart was all right. The operation was long, and the dissection was difficult because of the inflammatory changes around the hilus of the lung. Toward the end he had a sudden fall of blood pressure accompanied by bradycardia. We discussed with the anesthetist at that time the possibility of adrenal insufficiency, which Dr. Kranes mentioned. We gave him neo-synephrine, to which he had a favorable response. Postoperatively, when he again had a fall of blood pressure with bradycardia we thought of hemorrhage. But he had only a moderate amount of bloody fluid coming from his chest drainage tube. We gave him another transfusion, which did not affect his blood pressure. His bradycardia persisted. The cardiologist suggested that it was probably on the basis of myocardial failure. That is why an electrocardiogram was taken.

Dr. Richard Clark: There were two tracings done before the final episode. These are of value, primarily as showing nothing of great significance and as serving as a base line. This is the one taken after the operation, and it does show more than is described in the protocol. There is a distinct depression of the ST segment in Lead 1 of approximately 1 mm., a distinct elevation of the ST segment in Lead 2 of approximately 2 mm. and distinct elevation of the ST segment take off in Lead 3, whereas in Leads CF_2 and CF_4 there is significant depression of the ST segments. The T waves themselves are somewhat obscured by the superimposed P waves going with the auriculoventricular dissociation. I think this tracing is entirely consistent with an acute posterior myocardial infarction, which also involves the conduction system.

Clinical Diagnoses

Carcinoma of lung, right.
Right lower lobectomy, recent.
Coronary thrombosis.
Myocardial infarction, recent.

Dr. Davenport's Diagnoses

Bronchiogenic carcinoma.
Acute coronary occlusion.

Anatomical Diagnoses

(*Squamous-cell carcinoma of lung.*)
Operation: lobectomy.
Acute coronary thrombosis.
Myocardial infarct, recent.
Tuberculosis, old, bronchial lymph nodes.

Pathological Discussion

Dr. Castleman: Dr. Soutter removed the lower lobe with a portion of two ribs to which the tumor was adherent. In the center of the lesion was a necrotic cavity surrounded by irregular and nodular, granular tumor. Microscopically it was a squamous-cell carcinoma, Grade III. The regional lymph nodes showed no metastases, but there was old tuberculosis. The final affair, both as Dr. Clark and Dr. Davenport predicted, was an acute thrombosis of the right coronary artery. This vessel supplies the interventricular septum and posterior wall, which was infarcted. Microscopical examination of the infarct showed an extensive infiltration with leukocytes, such as one sees in an infarct about two days old. It would be interesting to decide whether this infarction could possibly have occurred before the operation or just before or even during the induction of anesthesia. I do not see how we can settle from the section of the myocardium whether it was thirty-six or forty-eight hours old. Certainly, it was within

that range. The polymorphonuclear leukocytes were still well defined and had not begun to degenerate very much. The myocardial fibers themselves were granular and had lost their striations. We found no metastases anywhere in the body.

CASE 35152

Presentation of Case

A seventeen-year-old grocery clerk was admitted to the hospital because of an abdominal mass.

The patient had been in excellent health until two months before admission, when he noted the onset of severe, gnawing pains coming on four to six hours after meals. These were confined to the left hypochondrium and relieved by food. Associated with this was regurgitation of food shortly after eating, which caused him to limit himself to a semiliquid diet. Three weeks prior to entry a mass was found in the left hypochondrium, and at about this time he complained of the feeling of food seeming to "stick" in the region of the umbilicus. He also passed two bulky, tarry stools following which he became progressively more constipated. One week before admission the onset of low thoracic back pain, more marked at night, was noted. Despite these symptoms and a weight loss of 15 pounds, his appetite remained excellent, and he continued his usual activities, such as playing hockey in the evening. There was no malaise, hematemesis or known fever. Four years before admission he had a seven-day episode of jaundice and clay-colored stools, both of which subsided spontaneously. The remaining past history was completely noncontributory.

Figure 1.

Physical examination revealed a well developed young man, showing some pallor and evidence of weight loss. The cervical and axillary lymph nodes were just barely palpable. The heart and lungs were normal. There was a large, hard mass in the left hypochondrium, filling the left upper quadrant. It was slightly tender and moved with respirations. The liver edge was palpable two fingerbreadths below the right costal margin. The right testicle and epididymis were enlarged, measuring together 5 by 4 by 3 cm. There was no history of injury, and the mass was nontender. The patient stated that one month before admission he had noticed the right testicle becoming larger than the left.

The temperature was 99°F., the pulse 100, and the respirations 18. The blood pressure was 130 systolic, 88 diastolic.

The urine showed a ++ test for bile and an occasional white blood cell. The blood hemoglobin was 10 gm. The white-cell count was 8000, with 86 per cent neutrophils, 6 per cent lymphocytes, 4 per cent monocytes, 2 per cent basophils and 2 per cent immature cells. The serum nonprotein nitrogen was 26 mg., and the total protein 5.7 gm. per 100 cc., the chloride 97 milliequiv. per liter, and the prothrombin time 20 seconds (control, 15 seconds). The stool was guaiac negative.

On the fourth hospital day gastroscopy was attempted, but neither the operative gastroscope (Benedict) nor the smaller gastroscope (Schindler) passed through the cardioesophageal junction. The cardiac orifice was dilated slightly with a No. 20 Fr. bougie, but no tumor could be seen. A roentgenogram of the chest showed a fine, strand-like increase in density throughout both lung fields. There was no enlargement of the hilar lymph nodes. There was an incidental finding of an old, healed fracture of the right tenth rib posteriorly. A gastrointestinal series showed a normal esophagus. There was a large, lobulated, firm mass surrounding the stomach and apparently inside the greater wall, extending from the fundus to the pylorus. Normal mucosal folds could be seen only in the extreme portion of the fundus. There were some very thick folds along the greater-curvature side (Fig. 1). A large, apparently intraluminal ulcer, 7 cm. in diameter, was present on the lesser curvature. There was no peristalsis, and the entire stomach was rigid, fixed and unpliable. There appeared to be enlargement of both liver and spleen. On the sixth hospital day an operation was performed.

Differential Diagnosis

Dr. J. Gordon Scannell: I think it is of considerable interest that there was a low lymphocyte count. It may be of significance.

Before looking at the x-ray films, which should be extremely helpful, we might review the history and see what definite leads we can get from the symptoms. Certainly, the patient had a good many symptoms involving the gastrointestinal tract. The pain, in a certain sense, could not have been more characteristic of ulcer, and he also had evidence of obstruction, although I would interpret the evidence of obstruction to be more indicative of motor disturbance of a large organ rather than obstruction distal to an organ that contracted. He did not have cramps, and he was without nausea, pain and real vomiting, although he had regurgitation of recently eaten food. He had some bleeding in the past presumably, and he certainly was anemic, which in a male patient connotes blood loss. It is interesting that he had a guaiac-negative stool in view of the fact that a large ulcer was visualized on x-ray study. He had lost weight; in spite of all this the appetite was good, which I think would be extremely unusual for a large, primary neoplasm of the stomach. The second lead, which occurs to me from the history, is the evidence of retroperitoneal involvement by whatever process we are dealing with. He had low dorsal pain, worse at night, which sounds as if he had something in the retroperitoneal area high up. Secondly, there is some evidence of biliary-tract obstruction, indicated by the fact that he had some bile in the urine. We wonder a little later if he had splenic-vein obstruction, with the enlargement of the spleen. The third obvious feature is the painless, nontender, testicular tumor coming on without antecedent history of trauma and attaining significant size in a short time.

The physical signs are important. There was essential absence of peripheral lymph nodes, so that would tend to steer away from the diagnosis of lymphoma. He had a large, hard mass in the left upper quadrant. This mass moved with respirations, which, I suppose, means that it was intraperitoneal in nature, although it seems to me difficult, with a large mass that has not a great deal of inflammatory fixation, to say that is necessarily so because I think a retroperitoneal mass, if large and nodular enough and not much inflamed, could move with respirations merely from the diaphragm downward. I am impressed by the description of the testicular tumor, which was localized to the testis itself and possibly the epididymis, did not invade the adjacent structures, and did not extend up the cord.

Dr. John M. Raker: It is only fair to note that the other testicle had the same consistence and was also slightly enlarged.

Dr. Scannell: I think I would rather have not known that. I have to now. The testicular mass was firm but not stony hard?

Dr. Raker: It was quite hard.

Dr. Scannell: The laboratory studies showed a lymphocytopenia, and I think that that might be indicative of low obstruction to the thoracic duct, which is one of the normal paths of the lymphocytes into the circulating blood. He had an anemia. We do not know the red-cell count, but probably do not need to. He had a ++ test for bile in the urine; unsupported by other evidence, I suppose that is indicative of some regurgitative type of jaundice. He might well have had a low-grade obstruction of the lower end of the biliary tract.

May we look at the x-ray films?

Dr. Stanley M. Wyman: The films of the chest show a possible minimal increase in the linear markings, but this is not very striking. I can see no localized disease in the lung fields, and the heart shadow is not remarkable. The old fracture of the right tenth rib is seen, and there is no evidence that this is pathologic. The strikingly abnormal stomach is well seen on this series of films, and the abnormality appears to extend from the extreme cardia to the immediate prepyloric region. The stomach maintains a constant contour, with very markedly thickened, irregular, possibly nodular, mucosal folds, with a tremendously large ulceration on the lesser-curvature side of the stomach, which appears to fall within the projected lumen of the stomach — at least in part. There is a suggestion, but nothing more definite, of a surrounding soft-tissue mass at several points in the stomach. The most important observation is the fluoroscopic observation that the stomach was rigid. The spleen can be faintly outlined, and it appears enlarged. The liver edge is less well visualized, and I am not so certain about the degree of possible hepatic enlargement.

Dr. Scannell: Your opinion is, then, that there is an intrinsic lesion of the stomach as well as extrinsic.

Dr. Wyman: I can see no definite evidence of an extrinsic lesion of the stomach, and I would call this intrinsic disease in the stomach itself, a process that infiltrates the entire stomach wall from the cardia to the prepylorus.

DR. SCANNELL: Could it be something growing through the stomach from outside in?

DR. WYMAN: I do not believe so, since it involves all the organ and seems to involve it rather uniformly. With something extrinsic I would expect it to involve one portion or another primarily.

DR. SCANNELL: You do not believe that something arising in the peritoneal cavity on the peritoneal coat of the stomach and invading the wall could give secondary changes in the mucosa?

DR. WYMAN: I do not believe it could be so extensive and so uniform. I would expect it to be localized to one region or another, probably on the lesser curvature.

DR. SCANNELL: I am getting more and more into deep water the more help I get.

I want to go back to the testicular tumor. There is no evidence of lymphatic blockage and no evidence of lymphatic metastases. In arriving at a diagnosis it seems reasonable to assume that the patient had a malignant lesion, and I think if it were not for the testicular tumor lurking malevolently in the background, one could make a strong case for a primary lesion in the stomach. These are admittedly rare in this age group but not unheard of. If it were a malignant tumor of the stomach, it would be something along the line of the lymphoma group — lymphoblastoma or something of that nature. But we have no other evidence of lymphoma, and it is very striking that these gastric symptoms are what they are if the tumor is primary there. Therefore, at a considerable risk, I am going to admit that it might be that, but I am more impressed by the testicular swelling and I think that the testicular tumor could give rise to these symptoms as given. I suppose, before going down farther, we should mention the other organs of the left upper quadrant, — the spleen, pancreas, kidney and left adrenal gland, — but there is no specific evidence to incriminate any of these. However, testicular tumor, as I would visualize it, would have to give rise to extensive retroperitoneal metastases in the region of the root of the mesentery, in the cisterna chyli and thoracic duct, and also peritoneal metastases to account for the picture as given. Of the testicular tumors, this is not an unlikely performance for a seminoma. I am using for my authority a recent report by Friedman and Moore* of some 922 cases studied in the Army Institute of Pathology, which recorded the accumulated experience of the last war. Friedman and Moore believed they could fit testicular tumors into four groups in which seminoma was as common as any other. They tended to occur later in life. They usually were restricted in that they did not invade massively at the local site but did tend to invade the retroperitoneal area and the peritoneal lining, which seems to have occurred in this patient. Other testicular tumors, which they group as embryonal carcinomas and which include the chorionepitheliomas, tend to invade locally and metastasize to the lung or liver. This patient did not show this. He had no secondary endocrine changes such as these patients frequently show or at least have demonstrated by urinary assay. A third type, which the authors report, are teratomas. These may be either adult, in which case they are considered relatively benign, or teratocarcinoma. Teratocarcinoma merely means a teratoid tumor in which definite malignant cells can be identified. These usually metastasize by virtue of their obviously malignant elements. They also metastasize to the parenchymal organs. The adult teratoma, which is usually benign, may metastasize as a relatively adult tumor, although this is comparatively rare.

I assume that, since Dr. Wyman has said that this probably was an intrinsic stomach lesion, I am displaying rank ingratitude to ignore it, but I think we can explain the picture on a seminoma, which developed massive retroperitoneal metastases in the region of the celiac axis and involved the stomach in the region of the cardia, where the stomach is really a retroperitoneal organ. The tight constriction, as it were, about the stomach would produce the secondary changes in the luminal portion.

DR. ALFRED KRANES: I do not quite understand why Dr. Scannell ruled out lymphoma.

DR. SCANNELL: I believe that we cannot rule it out. We have no other lymph nodes involved, but we do have a testicular tumor that could account for the symptoms.

DR. KRANES: The enlargement of the spleen?

DR. SCANNELL: The enlargement of the spleen could have been on the basis of obstruction of the splenic vein or retroperitoneal metastases.

DR. EDWARD B. BENEDICT: I would bet on a primary tumor of the stomach, partly on the basis of what Dr. Wyman describes and partly because when the gastroscope meets complete obstruction at

*Friedman, N. B., and Moore, R. A. Tumors of testis: report on 922 cases. *Mil. Surgeon* 99:573-593, 1946.

the cardiac orifice, it usually means primary tumor of the stomach.

Dr. Raker: The other testicle with the same consistence does not disturb you, Dr. Scannell?

Dr. Scannell: It disturbs me, yes.

Dr. Wyman: Roentgenologically, this picture is most consistent with lymphoma of the stomach.

Dr. Milford D. Schulz: To confuse the picture a little more, I looked at some films from this patient about an hour ago, and the stomach looks today not unlike what it did at the first examination here, after having been subjected to a period of two weeks of x-ray treatment. The patient received something like 1250 r in the region of the stomach, and there had been no demonstrable change.

Dr. Benjamin Castleman: This patient was operated on by a team of urologists and surgeons. Perhaps they can answer some of the questions.

Dr. Walter S. Kerr: When I saw him the right testicle was twice the normal size; the left testicle was normal. Two days later the right one had grown twice the size and the left one three times the original size — a matter of a few days. We explored the right testicle and found that it was involved by a uniformly appearing tumor. Dr. Moorman took over at that stage.

Dr. Henry D. Moorman: I explored the upper abdomen and took a biopsy from the involved wall of the stomach. The peritoneal cavity contained a large quantity of fluid, quite cloudy in appearance. The tumor seemed to arise intrinsically in the stomach in the sense that the tumor did not break out through the anterior serosal surface. We merely biopsied the anterior surface of the stomach because the whole mass was thick, and apparently all the retroperitoneal lymph nodes were involved.

Clinical Diagnoses

Gastric neoplasm, ? lymphoma.
Tumor of testis.

Dr. Scannell's Diagnosis

Seminoma of testis, with retroperitoneal metastases and extension into stomach.

Anatomical Diagnosis

Malignant lymphoma, reticulum-cell-sarcoma type, of testis, stomach and retroperitoneal lymph nodes.

Pathological Discussion

Dr. Castleman: We received a small biopsy from the stomach and the entire right testis. Grossly the testis had almost the same consistence of a normal testis, but on section the surface appeared to be uniformly replaced by a soft, pinkish-gray, obviously neoplastic tissue. Microscopically, however, the tubules of the testis persisted, and the tumor cells infiltrated between them without destroying them. In other words, the entire organ was not replaced by the tumor, but the tumor was interspersed between tubules, a finding very much against a primary tumor of the testis and more in keeping with a lymphoma, which is what this lesion was. It was a very rapidly growing lymphoma of the reticulum-cell-sarcoma type, and the biopsy from the stomach showed a similar appearance. We believe that lymphomas arise independently in various parts of the body rather than metastasize from one place to another. One can argue that this was primary in the stomach and metastasized to the testis, but it is more likely that it arose independently in the stomach, retroperitoneal lymph nodes and testis and apparently now in both testes.

A Physician: Are reticulum-cell sarcomas resistant to x-ray therapy?

Dr. Schulz: Ordinarily, no. Perhaps the reason why the lesion has not changed is that a sufficient amount of time has not elapsed.

Dr. Castleman: Are you using the 200 K.V. or the million-volt machine?

Dr. Schulz: The million-volt machine — it does not matter which one uses as long as it gets to the tumor. Of course, a larger dose can be given with the million-volt machine with less skin damage.

Dr. Donald S. King: How often do you see a lymphoma of the testicle?

Dr. Castleman: We have seen 2 cases, I believe, in which lymphoma was limited to the testicle, and I believe we have seen several cases with extensive disease throughout the body in which the testes were also involved.

Dr. King: It is uncommon, I should say.

Dr. Castleman: Yes. I believe that when lymphoma does occur in the testis, it is usually this type of lymphoma. I wonder if the immature cells seen in the peripheral blood were monocytes, which would fit in with this type of disease.

The New England Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. — Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. — John Fallon, M.D.

Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. — Donald Munro, M.D.
Henry Jackson, Jr., M.D.

Clara D. Davies, EXECUTIVE EDITOR
Robert O'Leary, ASSISTANT EDITOR

EDITORIAL BOARD

C. Guy Lane, M.D.	Maxwell Finland, M.D.
Henry R. Viets, M.D.	James M. Faulkner, M.D.
Robert M. Green, M.D.	Carroll B. Larson, M.D.
Dwight O'Hara, M.D.	Francis D. Moore, M.D.
Fletcher H. Colby, M.D.	C. Stuart Welch, M.D.
Robert L. Goodale, M.D.	Vernon P. Williams, M.D.
Chester M. Jones, M.D.	Benjamin Castleman, M.D.
Harvey R. Morrison, M.D.	Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS: $7.00 per year in advance, postage paid, for the United States (medical students, $4.00 per year); Canada, $8.00 per year (Boston funds); $9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS, *including those concerning classified advertising but not those regarding other advertising*, should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

NEW ENGLAND ADVERTISING REPRESENTATIVE (*except for classified advertising*): Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516.

THE SECOND MILE

THE way of the physician must in many respects be as pastoral as is that of the minister. Without the necessity of conforming to stated spiritual requirements, he, too, must act as guide and counselor, and seek to interpret life's enigmas when the need is greatest. For him, however, there is no congregation; his concern is primarily for the one, and only secondarily for the ninety and nine. Providing guidance, as he must, through the entire span of life, he attends man's entrance into it and supports his passage from it.

The true physician must introduce life to the world, moreover, with an assurance of its fruitfulness and, in complementary relation to the pastor, must many times help others to survey the dark and lonely valley in serenity and without fear. Having accepted the charge of going one mile with his neighbor he must then go with him twain. As Osler remarked in his Ingersoll Lecture on the Immortality of Man,* delivered at Harvard University in 1904, "The physician's work lies on the confines of the shadow-land, and it might be expected that, if to any, to him would come glimpses that might make us less forlorn."

In that same essay the Baltimore physician commented on the records he had kept of some five hundred deathbeds, describing the apparent sensations of the dying: although a small number suffered bodily pain or distress, very few indeed showed mental apprehension or terror. "The great majority gave no sign one way or the other; like their birth, their death was a sleep and a forgetting."

It is in the anticipation of death, then, rather than in the experiencing of it that man is particularly troubled, and this concern, with perhaps the majority of men, is as much over leaving the imperfect but familiar known, as it is over entering the unknown. Still, those of faith can better face that future with fortitude or even joy than can those who lack such transcendent strength.

It is in furnishing guidance down this last and lonely mile, however it may be numbered, that the true physician must develop and exercise one of his most valued skills. This is a skill that can be learned only through the lessons of experience, of compassion, of suffering with others, and of some personal compromise that has been effected between the known and the unknown. Lacking this skill and some form of religious belief, the doctor is only half a doctor — a guide for the first mile only.

All cannot have the supporting strength of a belief in a hereafter, but all can at least have hope and hopeful guidance when the lights grow dim, despite Osler's further statement: "The hopes and fears which make us men are inseparable, and this wine-press of Doubt each one of you must tread alone." This hope can, perhaps, be built up beyond man's fears, and bring each "to the opinion of Cicero, who had rather be mistaken with Plato than be in the right with those who deny altogether the life after death, and this is my own *confessio fidei*."

*Osler, W. *Science and Immortality. The Ingersoll Lecture, 1904.* 54 pp. Boston and New York: Houghton Mifflin Company, 1904.

STREPTOMYCIN-DEPENDENT BACTERIA

In the course of studies on the development of streptomycin resistance by meningococci during subcultures on streptomycin-containing culture plates, Miller and Bohnhoff[1, 2] observed the development of two types of variants. One, which they called Type A, appeared in approximately equal numbers for any given strain on all concentrations of the antibiotic, but the number of colonies per plate varied from strain to strain. It differed from the original culture in size and color of the colony and in being resistant to streptomycin in vitro and in vivo, but it multiplied on any medium that supported the growth of normal meningococci. It was as virulent for mice as the original culture from which it arose, and in animals it produced infection against which maximal doses of streptomycin afforded no protection.

Colonies of the second, or Type B, variant had one characteristic in common: they required streptomycin for reproduction in vitro and in vivo. This variant was not virulent for mice, in that mucin suspensions of the culture failed to produce infection on intraperitoneal inoculation as the parent strain did. However, mice inoculated in the same manner and treated with adequate amounts of streptomycin developed fatal meningococcal sepsis, and organisms could be cultured from the heart's blood on streptomycin-containing mediums but not on duplicate cultures on streptomycin-free mediums. The Type B colonies varied in size and color, depending on the concentration of streptomycin supplied.

Streptomycin-resistant and streptomycin-dependent variants have also been obtained by Paine and Finland[3, 4] from sensitive strains of a variety of different pathogenic organisms, including *Staphylococcus aureus*, *Escherichia coli*, *Proteus morganii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, and Yegian and Budd[5] obtained similar variants from a strain of *Mycobacterium ranae*, which is not a pathogenic organism. The former authors found that their truly resistant variants retained this characteristic on repeated subculture, either in the presence of streptomycin or in its absence, whereas prolonged incubation of the dependent organisms in streptomycin-containing mediums gave rise to either predominantly resistant or predominantly sensitive progeny, depending on the concentration of streptomycin contained in the medium. In most of these organisms, furthermore, there was little or no difference in the morphologic and cultural characteristics of the dependent and resistant variants, provided that an adequate concentration of streptomycin was present in the dependent variant.

Of additional interest is the fact that the dependent variant of *Myco. ranae* was found by Yegian and Budd to grow in the presence of streptomycin in medium containing 100 mg. per 100 cc. of sulfathiazole, whereas the parent strain and the streptomycin-resistant (Type A) variant were both inhibited by 1 mg. per 100 cc. of sulfathiazole. Their culture had not previously been exposed to sulfathiazole.

It is well recognized that the replacement of a streptomycin-sensitive by a streptomycin-resistant flora in the course of therapy renders useless any further treatment with streptomycin. The possibility that streptomycin-dependent organisms may arise and be maintained during streptomycin treatment, however, may constitute a more serious hazard. Although the continued streptomycin therapy may do no good against the usual streptomycin-resistant organisms, it is not likely to aggravate the infection or do any harm other than that resulting from the toxic effects of the antibiotic. The maintenance of streptomycin therapy in the presence of streptomycin-dependent organisms, on the other hand, might actually sustain or aggravate an infection by permitting the continued multiplication of these organisms when they would not otherwise multiply were the streptomycin therapy stopped. Furthermore, the appearance of streptomycin-dependent organisms in vitro is always accompanied by the occurrence of much larger numbers of resistant variants, so that, if the same principle is true in vivo, there seems to be no further reason for continuing streptomycin therapy after dependent variants have made their appearance.

The finding of streptomycin-dependent variants, apparently developing during treatment with streptomycin, has now been reported by two separate groups of observers.[6, 7] Spendlove et al.[6]

isolated a streptomycin-dependent strain of *Myco. tuberculosis* on the ninety-sixth day of streptomycin treatment. This was discovered during routine streptomycin sensitivity testing of the strains when it was noted that growth was poor in the control tube without streptomycin while it was abundant in all tubes containing streptomycin in concentrations ranging from 1 to 1000 microgm. per cubic centimeter. This patient's infection showed rapid progression during the course of streptomycin therapy, and no striking change occurred after this treatment was stopped.

In this case, a strain of tubercle bacillus isolated three months later had similar characteristics; it failed to grow in mediums without streptomycin and grew in the same mediums when concentrations of streptomycin from 1 to 1000 microgm. per cubic centimeter were added. If the findings as reported are correct they suggest either that the patient was supplying some factor that served in place of the streptomycin in supporting the multiplication of the dependent variants or that some of these variants arose during the course of the streptomycin treatment and persisted without multiplying in the patient after the antibiotic was discontinued.

More recently, Miller[7] looked for streptomycin-resistant or streptomycin-dependent organisms in animals and in patients under treatment with streptomycin. He gave normal rabbits and mice large doses of streptomycin and made periodic cultures of the pharynx and large bowel on mediums containing 400 microgm. of streptomycin per cubic centimeter. After a week both Type A and Type B variants were recovered in these animals. He made similar pharyngeal cultures on patients who were being treated with streptomycin and obtained positive cultures in 98 per cent of these patients by the thirteenth day of treatment. In addition, about 10 per cent of patients not receiving streptomycin and 4 per cent of the staff, students and laboratory personnel yielded a few organisms in similar cultures. The highest incidence of positive cultures among controls — 21 per cent — was obtained from the nurses and maids working on the wards. All the strongly positive cultures were from the nurses who were caring for patients receiving streptomycin. The organisms recovered from these cultures were predominantly the truly resistant or Type A variants, but a certain proportion were streptomycin-dependent or Type B.

These findings suggest that streptomycin-resistant organisms that developed in the throats of the treated patients were transferred to the nurses who looked after them. Although most of the organisms obtained in this study were presumed to be nonpathogenic, the possibility of transmitting resistant strains that are pathogenic is clearly evident.

Hobby and Dougherty[8] have described still another type of streptomycin-resistant variant capable of multiplying in an aqueous solution of streptomycin that contains no other added nutrients.

References

1. Miller, C. P., and Bohnhoff, M. Development of streptomycin-resistant variants of meningococcus. *Science* **105**:620, 1947.
2. *Idem.* Two streptomycin-resistant variants of meningococcus. *J. Bact.* **54**:467-481, 1947.
3. Paine, T. F., Jr., and Finland, M. Streptomycin-sensitive, -dependent, and -resistant bacteria. *Science* **107**:143, 1948.
4. *Idem.* Observations on bacteria sensitive to, resistant to, and dependent upon streptomycin. *J. Bact.* **56**:207-218, 1948.
5. Yegian, D., and Budd, V. Variant of *Mycobacterium ranae* requiring streptomycin for growth. *J. Bact.* **55**:459-461, 1948.
6. Spendlove, G. A., et al. Enhancement of growth of strain of M. tuberculosis (var. hominis) by streptomycin. *Pub. Health Rep.* **63**: 1177-1179, 1948.
7. Miller, C. P. Bacterial resistance to antibiotics. *Ann. Int. Med.* **29**: 765-774, 1948.
8. Hobby, G. L., and Dougherty, N. Isolation of streptomycin-resistant organism capable of utilizing streptomycin for growth. *Proc. Soc. Exper. Biol. & Med.* **69**:544-548, 1948.

MEDICAL DEFENSE BOTTLENECK

Doctor shortage in the armed forces is no longer news, but its importance is increasing so rapidly that the Secretary of Defense recently called a press conference to issue an urgent warning. He gave facts, stated alternatives and disclosed plans.

Owing chiefly to the expiration of ASTP and V–12 tours of duty, the armed forces, already numbering almost 1,700,000, will lack 2760 medical and dental officers by July and by December will lack 3600. "Normal procurement channels"— that is, the present volunteer system — offer the only means of making good this shortage, and January's record of 30 new Medical Corps and 20 new Dental Corps commissions may be taken as a fair sample of its inadequacy. "We are in grave trouble and it is getting worse" according to a memorandum to the Secretary of Defense from the Air Secretary, and "In the Army the situation is

more serious than in the Air Force" adds the Under Secretary of the Army. Failure to mention the Navy does not imply that the Navy is any more fortunate. Medical manpower is the bottleneck of the armed-forces expansion program, and a real solution must be found.

Four alternatives appear, of which only the fourth is presently favored by the Department of Defense. One is to ask for a draft of physicians and dentists in the numbers needed; the second is to request reserve officers who served in World War II to return to active duty; the third is to require the men now on active duty to remain after their time of service is up; and the fourth is to appeal to the 15,000 men who have not served, all of whom were deferred during the war and some of whom (8000) received part or all of their professional training at Government expense. The Secretary of Defense made the following statement:

> I believe these 15,000 men who saw no service overseas and who were not exposed to the rigors of war will themselves recognize our right to appeal to them to make a contribution in this emergency. . . . In a democracy, this procedure is fair, equitable, and just. . . . As Americans, I am confident that they will recognize their obligations if they are acquainted with the facts.

The Secretary is taking steps to implement these beliefs. By personal letter he will invite those trained at Government expense to accept commissions; through local professional leaders he will appeal to those who were deferred from the draft, and excused from combat to complete their professional education at their own expense, to apply for commissions; and by a publicity campaign he will enlist nation-wide support and understanding of the Defense Department's position.

An essential part of this program has been assigned to the Armed Forces Medical Advisory Committee composed of the surgeons general of the Army and Navy, the Air Surgeon, and eleven distinguished civilian doctors, under the chairmanship of Mr. Charles P. Cooper. Their task is to restore public confidence by eliminating professional manpower waste in the armed forces, thus removing the most serious stumbling block to voluntary service. It can be accomplished by merging the strength of the three services, by defining and streamlining their workload, by raising professional standards and by ensuring that "in so far as possible, each volunteer serves in an assignment commensurate with his professional skill and ability" so that his one or two years of military service will not be time lost. Should this immense undertaking succeed — and there is reason to believe that it will — a further debt of gratitude will be owed to the committee members, who, both in the regular components and as volunteers, have already rendered distinguished services to their country during the war.

Should this enlightened volunteer system fall short of meeting the manpower crisis, there will be no alternative but the draft, and whatever one may think of its fairness and its efficiency there will be no further possible doubt of its necessity. "For want of a nail the shoe was lost; for want of a shoe the horse was lost; for want of a horse the rider was lost" is the way *Poor Richard's Almanac* put it almost two hundred years ago. The modern version might read: for want of medical officers the armed forces were lost, for want of armed forces the peace was lost, and for want of the peace western civilization was lost. Whatever the price of success, one way or another it must be achieved now, for the price of another failure is too great for humanity to contemplate.

STUDY OF MATERNAL DEATHS

THE attention of fellows of the Massachusetts Medical Society and other readers of the *Journal* who reside and practice in Massachusetts is directed to the letter from Dr. Gillespie published elsewhere in this issue.

A five-year program has been initiated by the Committee on Maternal Welfare of the Massachusetts Medical Society, in conjunction with the Division of Maternal and Child Health of the Massachusetts Department of Public Health, for the study of all maternal deaths in the Commonwealth, whether they occur at home or in the hospital. All deaths within three months of the termination of pregnancy are to be included.

The purposes of the study are to determine exactly the total number of such deaths each year in the Commonwealth and the percentages at home

and in the hospital; to determine as exactly as possible the causes of all such deaths and their preventability; and to publish each year the number and causes, the findings of the study and the recommendations of the committee, both general and specific, for the improvement of maternal care.

So far as available statistics are concerned it is known that there were approximately 125 maternal deaths in the hospitals of the Commonwealth in 1948. It is not known with any exactness how many of the deaths at home took place before or after delivery and might be accountable to the pregnancy, nor is it known how many mothers died of contributory causes that might not be obstetrically listed. Thus, in the autopsy of sudden deaths suggestive of pulmonary embolism and thrombosis, the attention of physicians and pathologists is called to the possibility of amniotic-fluid emboli and the methods employed to prove such a diagnosis.*

The committee, in order that these important data may be obtained, strongly urges all physicians to report promptly to either physician mentioned in the communication all maternal deaths, wherever they may occur.

*Gross, P., and Benz, E. J. Pulmonary embolism by amniotic fluid. *Surg., Gynec. & Obst.* 85:315-320, 1947.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

CHISHOLM — Miles D. Chisholm, M.D., of Westfield, died on December 19. He was in his seventy-second year.

Dr. Chisholm received his degree from University College of Medicine, Richmond, Virginia, in 1900. He was formerly city physician in Westfield and was a member of the staff of the Noble Hospital. He was a fellow of the American College of Surgeons and the American Medical Association.

His widow, a daughter and two grandchildren survive.

CROSS — Albert E. Cross, M.D., of Worcester, died on November 6. He was in his seventy-seventh year.

Dr. Cross received his degree from Boston University School of Medicine in 1900. He was a member of the board of governors of the Hahnemann Hospital and was a member of the American Academy of Ophthalmology and Otolaryngology and the New England Ophthalmological Society and a fellow of the American Medical Association.

His widow and two daughters survive.

HEALY — James C. Healy, M.D., of Boston, died on November 19. He was in his forty-seventh year.

Dr. Healy received his degree from Tufts College Medical School in 1927. He was assistant professor of pharmacology at Tufts College Medical School.

His widow, a son and a daughter survive.

McKENZIE — John R. McKenzie, M.D., formerly of Cambridge, died on March 16. He was in his eighty-second year.

Dr. McKenzie received his degree from Harvard Medical School in 1894. He was formerly a member of the staffs of Holy Ghost Hospital for Incurables, Cambridge, and Worcester City, Boston City and Boston Lying-in hospitals. He was a fellow of the American Medical Association.

His widow and two sisters survive.

McQUADE — Lewis S. McQuade, M.D., of Quincy, died on March 10. He was in his sixty-seventh year.

Dr. McQuade received his degree from Tufts College Medical School in 1907.

A sister survives.

NEWELL — Franklin S. Newell, M.D., of Boston, died on March 3. He was in his seventy-eighth year.

Dr. Newell received his degree from Harvard Medical School in 1896. He was professor of clinical obstetrics emeritus, Harvard Medical School and Massachusetts General Hospital, a member of the American Gynecological Society and a fellow of the American Medical Association.

A sister survives.

PATTERSON — William F. Patterson, M.D., of Medford, died on February 23. He was in his eighty-third year.

Dr. Patterson received his degree from Tufts College Medical School in 1895. He was a fellow of the American Medical Association.

PEASE — Lewis W. Pease, M.D., of Weymouth, died on March 17. He was in his seventy-fourth year.

Dr. Pease received his degree from Tufts College Medical School in 1902.

His widow survives.

SEWALL — Edgar F. Sewall, M.D., of Somerville, died on March 22. He was in his sixty-fourth year.

Dr. Sewall received his degree from Tufts College Medical School in 1913. He was a fellow of the American Medical Association.

His widow, a son, a daughter, six grandchildren and a brother survive.

BOSTON MEDICAL LIBRARY

PORTRAIT OF SAMUEL DANFORTH

The portrait of Dr. Samuel Danforth (Harvard College, 1758), Paul Revere's physician, by Gilbert Stuart, owned by the Boston Medical Library, has been placed on exhibit in the Colonial Gallery of the Museum of Fine Arts through the courtesy of Mr. G. H. Edgell, director of the Museum. The portrait is on a temporary loan to the Museum. It is considered one of the better examples of the work of Gilbert Stuart.

MISCELLANY

MEDICAL DIRECTOR OF RED CROSS NATIONAL BLOOD PROGRAM

Dr. Louis K. Diamond, of Boston, has been appointed full-time medical director of the Red Cross National Blood Program. While discharging his new duties he will be on temporary leave of absence from the Children's Medical Center and the Harvard Medical School.

WATER POLLUTION CONTROL BOARD

Water-pollution control, for which an Act was passed by the Eightieth Congress, is gradually reaching the stage where definite action may be anticipated. The six non-Government members of the Water Pollution Control Advisory Board

have recently been appointed by the President, and in March the five Government members were selected by Federal Security Administrator Oscar R. Ewing.

The Board will assist in planning a program to support and promote technical research in water-pollution problems, "to provide federal technical services to State and inter-State agencies and to industries and to provide financial aid in the formulation and execution of projects for abatement of stream pollution."

CORRESPONDENCE

STUDY OF MATERNAL MORTALITY

To the Editor: Will you be so kind as to publish the following letter in a forthcoming issue of the *Journal*?

To the Hospital Administrator:

The Committee on Maternal Welfare of the Massachusetts Medical Society under the chairmanship of Dr. Duncan E. Reid, obstetrician-in-chief of the Boston Lying-in Hospital and professor of obstetrics at the Harvard Medical School together with the Division of Maternal and Child Health of the Massachusetts Department of Public Health, is initiating a five-year program for the study of all maternal deaths in Massachusetts as of January 1, 1949.

The Department of Public Health is financing this project through funds made available by the Children's Bureau and is vitally interested in obtaining the wholehearted support of this program from hospital administrators, all staff members of hospitals, and all practicing physicians in the Commonwealth.

For Worcester and all hospitals west of Worcester, the obstetrician in charge of this program will be Dr. Arthur F. G. Edgelow, 76 Maple Street, Springfield. His telephone number is Springfield 4-5926. For the eastern part of the state, which includes all cities and towns east of Worcester, Dr. Luke Gillespie, 1180 Beacon Street, Brookline, telephone Longwood 6-7773, will be in charge of the program.

Doctors Edgelow and Gillespie will assign an obstetrician to investigate promptly all maternal deaths which occur in the hospital or at home during pregnancy, delivery, or postpartum. These maternal deaths should be reported by telephone to either Doctor Edgelow or Doctor Gillespie immediately and should include the name and address of the patient, date of delivery, date of death, place of death, and the name, address, and telephone number of the physician who cared for the patient.

It is suggested that any physician who is in doubt as to the procedure should contact either Dr. Edgelow or Dr. Gillespie.

We would appreciate it very much if this letter could be read at your next regular staff meeting and then posted on your bulletin board. Enclosed duplicate is for your personal files.

Should there have been a maternal death in your institution since January 1 which has not been reported, would you please report it to either of the two obstetricians named above.

By direction of the Commissioner,
RICHARD P. MACKNIGHT, M.D., *Director*
Division of Hospitals

Commonwealth of Massachusetts
Division of Hospitals

LUKE GILLESPIE, M.D.

1180 Beacon Street
Brookline 46, Massachusetts

REGARDING MORAL PROBLEMS

To the Editor: I agree with Dean Sperry in his article in the *Journal* of December 23 when he says that life is sacred.

Why, may I ask, is life sacred? The answer must be that it is created by God — otherwise our premise does not hold. There, I think, we have the answer to the problems of both birth control and euthanasia.

Who are we to say when God shall give His gift or when He shall take it away? We boast of our scientific advances, which have resulted in a tremendous decline in maternal morbidity and mortality and also in a greatly increased life expectancy, and yet we find groups of physicians and clergymen advocating both birth control and euthanasia. To me it is not logical.

I believe that in matters of morals and ethics we should see things as black and white and not in shades of gray. In such matters we ought to be guided by the Ten Commandments rather than by the passing custom of the day.

MARGARET C. MCMANAMY, M.D.

Orange, Massachusetts

LOWER-NEPHRON NEPHROSIS VS. EXTRARENAL AZOTEMIA

To the Editor: Dr. James H. Townsend, in his reply to the letter of Walter Hollander, Jr., in the February 10 issue of the *Journal*, states that the distinction between extrarenal azotemia and lower-nephron nephrosis is largely an academic one: "We chose to call the disease extrarenal azotemia. If Mr. Hollander chooses to call it lower-nephron nephrosis, I should not object."

It appears to me that there are clinical and pathological differences between the two conditions.

Clinically, edema is an infrequent finding in extrarenal azotemia. In a review entitled "So-Called Extrarenal Uremia: A study of twenty cases," in the *American Journal of Medicine* (**5**:574-585, 1948), Murphy et al., eliminating cases in which vomiting was one of the major complaints, disclosed that in spite of more than an adequate fluid intake, orally and parenterally, edema occurred in only 2 cases. One patient had a + ankle edema due to heart disease, and the other had portal cirrhosis as demonstrated at autopsy. In lower-nephron nephrosis, edema generally develops, its severity depending upon the extent to which fluids had been pushed, as pointed out by Strauss in his study "Acute Renal Insufficiency due to Lower-Nephron Nephrosis," which appeared in the *New England Journal of Medicine* (**239**: 693-700, 1948). In extrarenal azotemia low blood pressure is practically always found. In Murphy's series only 1 patient had hypertension, and at autopsy he was found to have a chromophobe adenoma of the pituitary body. In lower-nephron nephrosis, after renal shutdown, the blood pressure rises, according to Strauss.

Any serious illness or injury may be the cause of extrarenal azotemia. In its pathogenesis the common denominator appears to be diminished blood flow through the kidneys. Lower-nephron nephrosis is produced by a wide variety of traumatizing conditions that have in common the main feature of shock.

Pathologically, in lower-nephron nephrosis, the lesions occur in a similar region in all the cases, with selective tubular damage to the ascending loop of Henle and the distal convoluted tubules. The glomeruli and the proximal tubules are only indirectly affected, as demonstrated by Hall and Luetscher in their review entitled "Renal Disease" in the *New England Journal of Medicine* (**239**:621-631, 1948). In a study of "Extrarenal Azotemia and Tubular Disease," which appeared in the *Journal of the American Medical Association* (**134**:441-446, 1947), Bell and Knutson found mild to severe hydropic degeneration of the *proximal* convoluted tubules in 20 of 84 cases. They suggested that the tubular injury was in part or entirely responsible for the uremia. In the remaining 64 cases there were no structural changes.

In the case cited by Appel and Townsend in their article "Extrarenal Azotemia: Report of a severe case with recovery," in the *New England Journal of Medicine* (**240**: 95-97, 1949), the patient was not in shock. He did not develop edema after the severe oliguria had begun, and the degree of hypertension (blood pressure of 144 systolic, 90 diastolic) was slight.

Like Drs. Appel and Townsend I choose to call the case one of extrarenal azotemia. However, I believe that the difference between lower-nephron nephrosis and extrarenal azotemia is more than an academic one.

JOSEPH G. WEINER, M.D.

Philadelphia, Pennsylvania

BRITISH VIEWPOINT ON BRITISH MEDICINE

To the Editor: If I have been somewhat tardy in writing this letter, it is because I am naturally hesitant to enter what is exclusively an American field. Medicine, however, knows no national boundaries, and I therefore feel constrained to present to my American colleagues my own interpretation of the situation in Britain, so vividly depicted by Dr. Sweet in his article in the February 3 issue of the *Journal*. Although I can quarrel with only a few of his facts, I find it difficult to believe that these have been viewed with the objectivity called for in Dr. Sweet's article.

Dr. Sweet considers the British National Health Service from the points of view of the specialist and the general practitioner, but he completely ignores that of the patient, who, I should have thought, would also have been interested. From all reports reaching me, the lay public in general is liking the Health Service very much indeed, and this is obviously a very important fact.

Great play is made by Dr. Sweet about the amount of form filling that a doctor has to carry out. There is a large amount, and nobody objects more than the doctor, but little of the increase is due to the Health Service, the main bulk arising from the shortages resulting from the war and from our subsequent dire economic situation. There is very little in the way of a black market in Britain, and the public at large prefers that necessities in short supply should be obtained by those most in need, rather than by those who can pay inflated or illegal prices. There are black sheep in every walk of life, and doubtless some doctors issue certificates on rather flimsy grounds, but it is a measure of the high esteem in which the medical profession is held by the public that doctors are asked to undertake so important if so irksome a duty.

I cannot agree that the doctor under the National Health Service is regarded by the patient, veteran or other, as being in some sort of sinister plot against him; in general, he is regarded as being impartial and fair-minded. As for the idea, advocated by Dr. Sweet, of a patient touting doctors until he finds one whose opinion can be bought, I can imagine nothing more damaging to the integrity and good name of the profession; Judas had his price.

A great deal of space is devoted by Dr. Sweet to describing the delay in providing a new building for a certain professorial department. These facts are only too true, — all such building in Britain is difficult to obtain, — but it is also true that a certain number of dwelling houses and other buildings were destroyed by bombs. Nothing undermines domestic morale more than sharing a house with another family, and I think it is reasonable that the highest priority should be given to domestic building.

Dr. Sweet also speculates about the amount of malingering that will be encouraged by a state health service. In fact all reports reaching me state that malingering is not a major factor. Almost all the new patients should have been seen long before, and most are very considerate and even rather embarrassed at either having to visit the doctor or having him to visit them — they know only too well how busy he is. Dr. Sweet's implication that doctors should only see those who think that their complaint might be trivial, provided such patients can pay suitable fees, falls right outside my conception of medical ethics; what is more important, it falls outside that of a large number of laymen and politicians. A properly trained doctor, however busy, is obviously better able to judge whether or not a complaint is trivial than a layman who is influenced by the size of his bankroll.

It is unquestionably true that panel practice in Britain is often very dreary, and a busy practitioner has to transfer to specialists many cases that in this country he might first attempt to deal with himself. A better system should undoubtedly be developed if it were possible, but against the discomfort of the overburdened general practitioner, one must weigh the advantage to the average patient of at least having an expert to decide whether he is seriously ill or not. Perhaps we are attempting to give the public a better service than the facilities and number of doctors permit; this is a matter on which the profession in this country might well ponder.

Please do not think that I necessarily endorse in full the National Health Service in Britain. There will obviously be very many teething troubles, but we shall ultimately make it work, though many heads may fall in the process, and though many aspects may have to be changed. I merely plead that these things be viewed as objectively as possible in their true context, since it is only by this means that you in America can derive benefit rather than harm from our experiment in Britain.

G. A. Smart

Massachusetts General Hospital, Boston

Dr. Smart's letter has been referred to Dr. William H. Sweet, who offers the following reply:

To the Editor: I am chagrined to learn that Dr. Smart interprets my statements to mean that patients should be encouraged to search out a doctor whose opinions can be bought or to consult one for trivial complaints if they can pay a fee. This is remote from the idea intended.

Dr. Smart's observation that the British people like their new health service is hardly astounding when one considers that it purports to relieve them of all responsibility in connection with illness and that only a tiny fraction of the expense of this service is borne by the direct health-insurance contributions of the person himself. The tentative conclusion to which I came however was that the doctor's colossal load under these conditions precluded efficient action by him — nor does Dr. Smart appear to challenge this.

He does condone grievous delays in vitally needed hospital construction even though patients on long waiting lists for admission to hospitals die in their homes before a hospital bed is available. He states "that the highest priority should be given to domestic building," because "nothing undermines domestic morale more than sharing a house with another family." For some time we in my family have been sharing our house with another couple and their children. Dr. Smart will perhaps be relieved to learn that the morale of the entire *ménage* remains excellent, and if this arrangement has by any chance hastened the completion of the new buildings of the Massachusetts General Hospital and the New England Center Hospital we are that much happier.

William H. Sweet

Boston

REGARDING THE FARREN HOSPITAL EPISODE

To the Editor: With the summary administrative dismissal of 4 members of the Franklin District Medical Society from the medical staff of the Farren Memorial Hospital in Montague City, Massachusetts, in the three days before the election in November, 1948, a total of 20 doctors have lost their hospital privileges in western Massachusetts for publicly approving the "Birth Control" referendum on the Massachusetts ballot. The others were 12 in the Pittsfield area in 1942, and 4 in the Springfield area in 1946.

The first amendment to the constitution of the United States seems to guarantee the right of free speech without penalty; the citizens of Massachusetts in the same election overwhelmingly voted reapproval of this guarantee; the Massachusetts Supreme Court had certified this referendum to the ballot for public discussion and vote; and no promise, either written or oral, had ever been requested of any of these doctors before in connection with this amendment. The medical-staff by-laws have no such requirements. No hearing, either before or after dismissal, has ever been granted. No doctor has ever been reinstated except by signing a new application blank, which included a promise not to exercise this right of free speech; 4 doctors in the Pittsfield area have made this promise.

As president of the Franklin District Medical Society I held several consultations with the Sister Superior, and with 2 members of the Executive Committee of the Trustees; two committees of the Society held meetings during the month of November, one of them with the hospital authorities. An energetic petition supporting reinstatement was voted by the Society and presented to the Board of Trustees. In spite of this abridgment of civil rights the petition was not even placed on the agenda for the meeting by the President. A petition by me as a twenty-year member of the Farren Memorial Hospital medical staff and simultaneously president of the District Medical Society was sent to the Most Reverend A. G. Cicognani, the Apostolic Delegate in Washington, and its receipt has been doubly verified. With the passage of several weeks, even with a follow-up letter, no answer has been received.

The situation in this district is different from that in others, in that alternate hospital facilities are limited. There is only one other hospital. Total county bed capacity is below requirements, and will remain so for several years. In addition, the Farren Memorial Hospital was built in 1900 by a private citizen, Bernard N. Farren; it was given to a Massachusetts tax-free public charitable corporation; he was so determined that it should only be used as a hospital that he had this legal restriction filed in the Registry of Deeds; he repeated this and added a further legal limitation in 1910; the Board of Trustees consisted, and still does as a continuing policy, of both Catholic and Protestant members; the Sisters of Providence act as the supervising agents; the hospital has always admitted patients of any race, creed and color; the hospital has been supported in part by all races, creeds and colors as a result of campaign for funds by the hospital; and doctors have always been selected on the basis of professional qualifications and abilities.

The dismissed doctors and a majority of the Franklin District Medical Society believe that admission to and dismissal from the staff of this hospital should still be based exclusively on professional qualifications and abilities. A large element of the community, who have supported the hospital without favoritism and whose hospital care has been jeopardized because of this further restriction of hospital medical care, support this stand. It is believed therefore that this report to the medical fraternity in Massachusetts should be made.

LAWRENCE R. DAME, M.D.

Greenfield, Massachusetts

SMOKE GETS IN ONE'S EYES

To the Editor: Since the medical profession as a group seems to be on trial because of its reactionary conservatism and its adherence to the *status quo*, perhaps one more item of cricitism is in order.

One wonders if the editor, because of the remunerative advertising by the cigarette interests and because perhaps the medical profession are as a group the greatest consumers of cigarettes, would venture to publish the enclosed clipping by a recognized authority, in the interests of cancer control.

> Excessive smokers are four times as liable as nonsmokers to have cancer of the mouth and respiratory system, and even mild smokers are twice as vulnerable to the disease as persons who do not smoke, according to Dr. Herbert L. Lombard, director of the Cancer and Chronic Disease Division, Department of Public Health. — *Needham Chronicle*, March 16, 1949.

J. WALTER SCHIRMER, M.D.

Needham, Massachusetts

NOTE: The editor is required to take far bolder steps than this. — ED.

DEPRIVATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held March 24, it was voted to revoke the registration of Dr. Louis R. Medverd, 1210 Cambridge Street, Cambridge.

GEORGE L. SCHADT, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

AN OPEN LETTER

To the Editor: A most critical professional manpower shortage is facing the medical departments of the armed forces. The urgency of the need for physicians and dentists can be judged from the fact that by July of this year the armed forces will have lost almost a third of their present staff of physicians and dentists. The tours of duty of these professional men will expire, and normal procurement measures cannot fill the vast number of vacancies that will arise.

By the end of July we shall be short about 1600 physicians and 1160 dentists. By next December this shortage will grow to 2200 physicians and 1400 dentists. This means that the armed forces will not have enough professional men to give minimum medical service to almost 1,700,000 men and women who are serving their country.

You and your publication have been asked many times for assistance in special drives and campaigns for the welfare of our country. You have at all times shown whole-hearted co-operation.

We have sought and received support in this campaign from the professional societies from the national to the community level. Deans of medical and dental schools and the heads of hospitals have also been asked to co-operate in this emergency.

The success of this procurement campaign will depend primarily upon public understanding and public support. The people of the United States must be made aware of the seriousness of the problem that faces us. If this shortage is allowed to develop, it could jeopardize our entire national defense program.

The medical departments of the armed forces and the Government ask your co-operation in averting a situation that could have serious effects on the security of this country. Through your editorial pages and news columns you can help us inform the people of this country of the vital needs of the medical departments of the armed forces. You can urge young men who received their medical and dental educations during the war years, and who have given no service, to volunteer their services to their country now when the need is so great.

It must be made clear that we are not asking for physicians and dentists from areas where a shortage already exists. We are only trying to replace the physicians and dentists who have completed their obligation and who will be relieved from duty with the armed forces and will return to civilian life to practice their professions.

Your co-operation in this campaign can be of inestimable value and will be greatly appreciated by the medical departments of the armed forces, the young men and women in our armed forces and the families of these young people.

JAMES FORRESTAL

Office of the Secretary of Defense
Washington

BOOK REVIEWS

The Battle of the Conscience: A psychiatric study of the inner working of the conscience. By Edmund Bergler, M.D. 8°, cloth, 296 pp. Washington: Washington Institute of Medicine, 1948. $3.75.

The title and subtitle of this work lead one to believe that here at last is a full-length study of a controversial and highly important subject. Instead, there are a number of related but, unfortunately, not fully integrated chapters — each almost complete in itself — in which the role of conscience is studied only as it pertains to the topic under discussion. Frequently, greater emphasis is placed on other studies of the author, with especial emphasis on the triad of the mechanism of oral erotism (as the basis for neurotic symptoms), and for sublimation a five-layer structure is alleged to exist.

Granting such possible mechanisms, one remains unimpressed about the designated numbers or strata as such. Clinical experience convinces one that such categories, although convenient, rarely exist, and this is not too strange since undoubtedly neither psychiatrist nor analyst ever succeeds in learning even an infinitesimal part of the dynamics of the mind (the thought process, the conscience) at either conscious or unconscious level.

Similar criticism can be made of the author's designation of magic gestures with completely different meanings. The fact that he designated various types under the term "magic gesture" will not succeed in preventing confusion in the literature because it is reasonable to assume that the term will be frequently used and its meaning will not always be clear.

An apology is made that analytical material is scant in criminal cases because some millionaire has failed to donate funds for such a study — a candid, but disheartening admission, when one recalls that scientists in other fields have devoted years of study without thought to monetary reward. This has been true particularly in the medical world and applies not only to research but also to care of the sick. Therefore, one might suppose that despite the lack of funds for 50 experienced analysts to devote themselves exclusively

to the study of criminals, perhaps each analyst might feel honored to participate in such a study by devoting a "free hour" to the purpose.

Apart from these few criticisms, the book makes good reading; the examples cited are typical, and sources of other works are clearly acknowledged. The author's style remains clear, but by now, this is taken for granted in any of Dr. Bergler's books.

The Driving Forces of Human Nature and Their Adjustment: An introduction to the psychology and psychopathology of emotional behavior and volitional control. By Thomas V. Moore, Ph.D., M.D. 8°, cloth, 461 pp., with 26 illustrations. New York: Grune and Stratton, 1948. $6.50.

In this work the author presents a compilation of some of the more important aspects that are at present acceptable in the study of the forces concerned in human behavior. The author draws upon his obviously extensive and broad cultural background to clarify his position, and colors the entire work with a religious (Roman Catholic) texture. It is in essence a psychologic, philosophical work in which he draws upon examples both in experimental psychology and in psychiatric therapy. He touches on various theories concerned in the dynamics of human behavior and, for the most part, maintains a "middle of the road" position regarding dynamic theories, reserving as his ultimate solution that of religion. He presents numerous case studies and methods of treatment concerning these cases, choosing them carefully to illustrate his point of view. As an introduction to the problems of human nature, the book presents a wealth of material both historically and analytically.

Physiology of Exercise. By Laurence E. Morehouse, Ph.D., and Augustus T. Miller, Jr., Ph.D. 8°, cloth, 353 pp., with 51 illustrations and 10 tables. St. Louis: C. V. Mosby Company, 1948. $4.75.

This book attempts to give the fundamental facts of physiology as they concern exercise. It is written primarily for teachers of physical education and practitioners of physical medicine. The material is presented in a simple, easily understood style. A glossary at the end of the book explains the technical terms that have been used. The chapters on physical fitness and on training should be of particular interest to physicians. This book can be recommended as a helpful volume containing the essential data on the physiology of exercise.

Psychic Energy: Its source and goal. By M. Esther Harding, M.D., M.R.C.P. With a foreword by C. G. Jung. 8°, cloth, 497 pp., with 5 illustrations and 9 plates. New York: Pantheon Books, 1947. $4.50. The Bollingen Series X.

In this book the author, via a Jungian delving into the "unconscious," attempts to answer the query whether or not the primitive and "unconscious" side of man's nature can be tamed effectively or even altered. She believes that contemporary culture and civilization afford but a poor façade covering unconscious roots that are essentially base, vile and self-annihilating. Such a façade is superficial and vulnerable, and men must regress to primitive levels of the unconscious, as seen in the totalitarian rationalization and the world conflicts of today. The author holds out little hope of changing the "collective unconscious" of a people, but individuals may be saved and thus possess "the germ of a renaissance of the spiritual values of mankind."

The author draws freely upon the art and literature of various cultures in support of her theses, but this seems to serve only the more to leave the reader with the sensation of having viewed a séance of religious mysticism. The book is as pessimistic and ethereal as anything Jung himself might have written. One gathers that peoples, as such, are doomed, condemned even pre-partum by the "collective unconscious"; salvation there is for an accidental few who can be led, through the means of "analytical psychology," to wallow in the "unconscious" and be led therefrom again chaste and pure in heart and mind.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

De beteekenis van de lymphklier-punctie voor de diagnostiek van perifere lymphklierzwellingen. By L. B. J. Stuyt. Academisch Proefschrift, Universiteit van Amsterdam, 1 Juli, 1947. 8°, paper, 110 pp., with 31 illustrations. Amsterdam: Scheltema & Holkema's Boekhandel, 1947.

In this monograph, which was presented as a thesis for the degree of doctor of medicine at the University of Amsterdam in 1947, the author discusses puncture and aspiration of swollen lymph nodes for the purpose of obtaining material for cytologic diagnosis. The text is based on the experience of the author with over 300 patients and on the literature on the subject. The author indicates that the method may be used when biopsy is contradicted, that it is possible to identify cell pictures in a number of conditions and that the procedure may be used as often as desired and as a control on therapy; he recommends that the method be adopted as routine in the differential diagnosis of enlargement of the peripheral lymph nodes. The material is well organized, discussing in order the anatomy and physiology of the lymph nodes, and their pathological anatomy, the clinical diagnosis of enlargement of the peripheral lymph nodes, the technic of puncture and its diagnostic value. The text is in Dutch, with summaries in English and French. A bibliography is appended to the text. The type, printing and illustrations are excellent.

Racial Variations in Immunity to Syphilis: A study of the disease in the Chinese, white and Negro races. By Chester N. Frazier, M.D., Dr.P.H., and Li Hung-Chiung, M.D. 8°, cloth, 122 pp., with 27 tables. Chicago: University of Chicago Press, 1948. $2.50.

In this monograph the authors analyze 16,845 consecutive cases of syphilis in the Chinese, white and Negro races. The study points out that regardless of race or sex the disease was essentially the same in all people and that the differences between races lay almost entirely in the relative frequency of the development of the disease. A bibliography and a good index conclude the volume.

Advances in Pediatrics. Editorial Board: S. Z. Levine, M.D., Cornell University Medical College, New York, Allan M. Butler, M.D., Harvard Medical School, Boston, L. Emmett Holt, Jr., M.D., New York University, College of Medicine, New York, and A. Ashley Weech, M.D., University of Cincinnati, College of Medicine, Cincinnati. Volume III. 8°, cloth, 363 pp. New York: Interscience Publishers, 1948. $7.50.

This third volume of an important series presents eight papers by different authors of interest to pediatricians and physicians concerned with the diseases of children. The papers comprise the effects of birth processes and obstetric procedures upon the newborn infant; retrolental fibroplasia, emotions and symptoms in pediatric practice; therapeutics of epileptiform seizures; viral hepatitis; abnormalities of sexual development during childhood and adolescence; psychological considerations of puberty and adolescence; and the osteochondroses. The papers present the up-to-date knowledge on the particular subjects under consideration. Comprehensive bibliographies are appended to the various papers. There are good indexes of authors and subjects and the volume is concluded with a cumulative index of authors and subjects for volumes 1 to 3. The type and printing are good, but the heavy, coated paper is unnecessarily used, making the volume too heavy for its size. It should be remembered that when this type of paper becomes wet by accident the volume is transposed into a block as hard as concrete. The series is valuable and should be in all medical libraries and in the collections of physicians interested in pediatrics.

Trabajos del Dispensario Antituberculoso Central y del Sanatorio Antiberculoso de Ofra de Santa Cruz de Tenerife, Canarias, Espana. Director: Dr. T. Cerviá. Volume VIII, Anos 1946–47. 8°, paper, 245 pp., illustrated. Santa Cruz de Tenerife: Imprenta Católica, 1948.

This report is divided into two parts, the first comprising the statistics of the sanatorium for the years 1946 and 1947, and the second consisting of a series of clinical papers by director Cervia and his assistants on the various aspects of tuberculosis. The text is concluded with a poem by Dr. J. Duran, entitled *Cantar del buen bacilo.* The volume constitutes a valuable addition to the literature of tuberculosis, and the series should be in all collections on the subject and in reference and research medical libraries.

Textbook of Surgical Treatment, including Operative Surgery. Edited by C. F. W. Illingworth, C.B.E., M.D., Ch.M., F.R.C.S.E., Regius Professor of Surgery, University of Glasgow. Compiled by twenty-one contributors. Third edition. 8°, cloth, 644 pp., with 289 illustrations. Baltimore: Williams and Wilkins Company, 1947. $10.00.

This collected work by twenty-one contributors has been revised and brought up to date. Four contributors have been added to the authors. The chapter on wounds and wound infections has been rewritten, and sections added on penicillin in surgery, plastic surgery, rehabilitation and faciomaxillary injuries. New material has been incorporated on the use of protein in surgery, the Rh factor and the anticoagulant treatment of thrombosis. Fifty-nine illustrations have been added. The work is of British origin and is well published in every way. It is recommended as a reference text for all medical libraries and surgeons.

Recent Advances in Surgery. By Harold C. Edwards, C.B.E., M.S., F.R.C.S., surgeon and lecturer in surgery, King's College Hospital, London, surgeon to the Evelina Hospital for Sick Children, and dean of the medical school, King's College Hospital. Third edition. 12°, cloth, 437 pp., with 131 illustrations. Philadelphia: Blakiston Company, 1948. $6.50.

The first edition of this reference book was published in 1928, the second edition of 1929 was translated into Spanish, and this third edition has been revised to bring the material up to date. Short lists of references are appended to the various chapters. The material is well organized and is arranged by divisions of the body. Short lists of references are appended to the various chapters. It is a British book, printed in Great Britain, and well published. The plates are separately inserted in the text. The volume should be in all medical libraries and should prove useful to surgeons.

Oral and Dental Diseases: Aetiology: histopathology, clinical features and treatment. A textbook for dental students and a reference book for dental and medical practitioners. By Hubert H. Stones, M.D., M.D.S., F.D.S.R.C.S.Eng., professor of dental surgery and director of dental education, University of Liverpool, and consultant, E.M.S. Maxillo-facial Centre, Broad Green Hospital, Liverpool. 8°, cloth, 896 pp., with 926 illustrations. Baltimore: Williams and Wilkins Company, 1948. $18.00.

This volume constitutes a comprehensive treatise on the diseases of the mouth, jaws and teeth. The material is well organized. There is a long chapter on oral tumors and one on the diseases of the salivary and oral mucous glands. Lists of references are appended to the various chapters. The text is well printed with a good legible type. Comprehensive indexes of authors and subjects conclude the volume. The treatise is British and printed in Great Britain. It is recommended for all medical libraries and should prove valuable to all dentists and to physicians interested in the subject.

Retropubic Urinary Surgery. By Terence Millin, M.A., M.Ch.(Dubl.), F.R.C.S., F.R.C.S.I., surgeon, All Saints' Hospital for Genito-Urinary Diseases, London, genitourinary surgeon, Royal Masonic Hospital, London, urologist, Surrey County Council, and genitourinary surgeon, Chelsea Hospital for Women, London, Southall-Norwood and Cray Valley hospitals. 8°, cloth, 208 pp., and 163 illustrations. Baltimore: Williams and Wilkins Company, 1947. $7.00.

This monograph describes the author's methods of retropubic approach for prostatic surgery. Included is his hitherto unpublished operation for stress incontinence in women, first used in 1944. An appendix lists fifty consecutive one-stage retropubic prostatectomies. A good index ends the text. The book is of British origin and is well published. It should prove valuable to all surgeons interested in the subject.

A Course in Practical Therapeutics. By Martin E. Rehfuss, M.D., professor of clinical medicine and Sutherland M. Prevost Lecturer in Therapeutics, Jefferson Medical College, Philadelphia, and attending physician, Jefferson Medical College Hospital, Philadelphia; F. Kenneth Albrecht, M.D., and Alison H. Price, M.D., assistant professor of medicine, Jefferson Medical College, Philadelphia, and assistant physician, Jefferson Medical College Hospital, Philadelphia. 4°, cloth, 824 pp., with 70 plates. Baltimore: Williams and Wilkins Company, 1948. $15.00.

This joint work of thirteen clinicians covers the whole field of therapeutics in a practical manner. The text is divided into four large sections comprising general therapeutic principles, symptomatic therapy, treatment of specific disorders and special treatment. The symptoms discussed in the second part are arranged alphabetically. The various diseases and conditions in the third part are arranged by the systems of the body or by classes of diseases. The treatment of each disease is preceded by a concise description of the etiology, pathology and symptomatology. The treatment is extensive in scope. The material is well arranged, and the text is well printed with a good type in two columns on good paper. A comprehensive index concludes the volume. The inside front and back covers are used for valuable tables on normal values in blood constituents and metric and apothecary doses. This is a poor practice because anything printed on the covers becomes defaced and worn from usage of the volume. The book should prove valuable to physicians in their daily work, and as a reference work for medical libraries.

Human Nutrition. By V. H. Mottram, M.A. (Cant.). 12°, cloth, 151 pp., with 9 illustrations. Baltimore: Williams and Wilkins Company, 1948. $2.75.

This popular manual on human nutrition is written by an eminent British scientist. The material is well arranged and written in a simple, easy style. The fundamentals of dietetics, food hygiene and cooking and processing and storage of foods and proteins, minerals and the vitamins are considered in various chapters. There are also chapters on normal dietetics, digestion, absorption and metabolism of food, and on the nature of foods, comprising analyses of the common foods. The chapter on the optimal diet is gauged to present British conditions. A good index concludes the text. The volume is well published.

Treatment by Manipulation in General and Consulting Practice. By A. G. T. Fisher, M.C., M.B., Ch.B., F.R.C.S.(Eng.), orthopedic surgeon to the rheumatic unit, St. Stephen's Hospital. Fifth edition of *Manipulative Surgery.* 8°, cloth, 275 pp., with 126 illustrations. New York: Paul B. Hoeber, Incorporated, 1948. $5.00.

This book was first published in 1925 under the title of *Manipulative Surgery.* In this fifth edition much material has been added, and forty-five new illustrations have been included. Many sections have been rewritten and expanded to incorporate the advances in knowledge made since the fourth edition of 1944. Emphasis has been placed on the treatment of crippling deformities of rheumatic disease. The objective of the work is to emphasize the value of manipulative treatment in carefully selected cases of certain sequelae of injuries and diseases affecting the joints, muscles, tendons and fasciae. The various chapters discuss the pathology of the joints, prevention and diagnosis of adhesions and manipulative treatment in general and of the upper and lower extremities, the spine and the sacroiliac joint. The concluding chapters consider the dangers of manipulation in unsuitable cases, aftertreatment and osteopathy. The book is of British origin and printed in Great Britain. The publishing is well done, and the illustrations are excellent. The volume should be in all medical libraries and should prove useful to orthopedists.

Textbook of Chiropody. By Margaret J. M. Swanson, B.Litt., F.Ch.S., co-founder of Edinburgh Foot Clinic and School of Chiropody. 8°, cloth, 212 pp., with 168 illustrations. Baltimore: Williams and Wilkins Company, 1948. $5.00.

This short treatise on chiropody as a specialty also considers the medical and surgical conditions met with in practice that should be referred to competent specialists. The text is well written in a scientific manner, and the material is well arranged. The publishing is excellent and was done in Great Britain. The illustrations are also excellent. A glossary of terms concludes the text. There is a good index. The book is recommended to medical libraries and to all persons interested in the subject.

Principles and Practice of the Rorschach Personality Test. By W. Mons, M.R.C.S., L.R.C.P., Lt.-Col. R.A.M.C., adviser in psychiatry, South East Asia Command. 8°, cloth, 164 pp. Philadelphia: J. B. Lippincott Company, 1948. $4.00.

This manual on the Rorschach ink-blot test is intended as an introduction to more advanced works and is based on ten years' experience, including examination of 1000 children, aged four to sixteen years, and divided into two equal groups of normal and subnormal children. There is a good index, and the publishing is excellent in every way.

Standards for the Diagnosis and Treatment of Cancer. By the Cancer Committee of the Iowa State Medical Society. 8°, paper, 160 pp. Iowa City, Iowa: Athens Press, 1948. $1.00.

This manual was first published in 1937. During the following eleven years over fifty thousand copies were printed and distributed to the medical profession of Iowa and nearby states. This second edition has been revised to bring the subject up to date. The text is divided into a number of short, concise chapters on the diagnosis, treatment and prognosis of cancer of the various organs and structures of the body. Under diagnosis the early and late signs and differential diagnosis are considered. Two preliminary chapters discuss general considerations and the cancer problem and the family doctor. The final chapter is on radiation therapy in general. An extensive bibliography arranged by chapters concludes the text. The manual is well published in every way and should prove valuable as a compendium for practicing physicians.

Microbiology and Pathology. By Charles F. Carter, M.D., instructor in pathology and applied microbiology, Parkland Hospital School of Nursing, Dallas, Texas, director, Carter's Clinical Laboratory, Dallas, consulting pathologist, St. Louis Southwestern Railway Hospital, Texarkana, Arkansas, and consulting pathologist, Mother Frances Hospital, Tyler, Texas. Fourth edition. 8°, cloth, 845 pp., with 216 illustrations. St. Louis: C. V. Mosby Company, 1948. $5.00.

Dr. Carter, in this new edition of his standard textbook, first published in 1936, has thoroughly revised the text to bring it up to date. The section on microbiology has been entirely rewritten, incorporating the great advances in knowledge in the field since the publication of the third edition in 1944, including the use of the sulfonamides and the antibiotics. A chapter on immunization has been added. The section on pathology has been largely rearranged and rewritten. Infectious hepatitis and homologous serum jaundice have been discussed, and new chapters on the hospital pathologist and his work, and on defects of body development have been included. Lists of selected references have been appended to the various chapters. The text is concluded with a chapter on laboratory exercises and a glossary of terms. There is a good index. The book is designed for the use of schools of nursing and nurses, and the need of four editions speaks well for its soundness.

Preoperative and Postoperative Care of Surgical Patients. By Hugh C. Ilgenfritz, M.D. With a foreword by Urban Maes, M.D., D.Sc. 8°, cloth, 898 pp., with 110 illustrations. St. Louis: C. V. Mosby Company, 1948. $10.00.

This treatise is comprehensive in scope. The early chapters deal with general subjects such as fluid and electrolyte balance, metabolism and nutrition, shock, transfusion, sedative medication, systemic and organic complicating factors, chemotherapy, general measures, minor and major postoperative complications, care of the wound and burns. The later chapters consider the various organs and regions of the body. A comprehensive index concludes the volume. The type and printing are excellent, but the use of a heavy filled paper is not justified by the text. The book should prove useful to surgeons and as a reference work for medical libraries.

More Than Armies: The story of Edward H. Cary, M.D. By Booth Mooney. With an introduction by Dr. Morris Fishbein. 8°, cloth, 270 pp. Dallas, Texas: Mathis, Van Nort and Company, 1948. $5.00.

This biography of Dr. Cary is written in a narrative style by a trained journalist. Dr. Cary has been interested in medical education for many years and has been closely associated with the American Medical Association for thirty-five years, serving as trustee for five years and as president of the Association in 1933. He is a past president of the Southern Medical Association. He served for a number of years as dean of the Medical School of Baylor University and, in 1943, founded the Southwestern Medical College. He is a distinguished ophthalmologist. The book is well published, but the lack of chapter headings detracts from its reference value, and the price of five dollars seems high for the volume. It is recommended for all medical-history collections.

Take Off Your Mask. By Ludwig Eidelberg, M.D. 8°, cloth, 230 pp. New York: International Universities Press, 1948. $3.25.

This small volume depicts an imaginary working day of a psychoanalyst. Seven case histories are presented, dealing with different kinds of psychic disturbance. These cases are not actual but are built up to portray ideal examples of the condition under discussion. One chapter is devoted to a training analysis. The book is semipopular and should prove useful to persons interested in the subject.

Eskimo Doctor. By Aage Gilberg, M.D. Translated by Kaaia Elliott. 8°, cloth, 229 pp., illustrated. New York: W. W. Norton and Company, Incorporated, 1948. $3.00.

This is the story of a young Danish physician who went to be the community doctor for an isolated group of polar Eskimos in Thule, Greenland, the northernmost human settlement in the world. Dr. Gilberg tells of the day-to-day life of himself and his wife, describing his adventures while he was ministering to the people scattered over a large area, and the character and customs of the Eskimos. The story is well told in an easy, narrative style. The book is translated from the original Danish. It is recommended for all medical-history collections and to all persons interested in the history of medicine. It is a fine piece of work.

NOTICES

MASSACHUSETTS ASSOCIATION OF MEDICAL TECHNOLOGISTS

The state conference of the Massachusetts Association of Medical Technologists will be held at Horticultural Hall, Elm and Chestnut Streets, Worcester, on Saturday, April 2[illegible].

PROGRAM

10:00 a.m.–12:00 m. Business meeting and nomination of state officers (Mrs. Eichman, of the American Society of Medical Technologists, will be the speaker).

12:30 p.m. Lunch.

2:00–3:00 p.m. Newer Serologic Technics for Isoantibodies. Dr. Victor Vaughan, III.

3:00–4:00 p.m. Registry: Its standards and how to meet them. Dr. Donald Nickerson.

(*Notices concluded on page xv*)